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Distribution of Paroxetine in Postmortem Fluids and Tissues

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16. Abstract

Paroxetine is a selective serotonin reuptake inhibitor that is a commonly prescribed drug for the treatment of depression, obsessive-compulsive disorder, panic disorder, social anxiety disorder, premenstrual dysphoric disorder, and post-traumatic stress disorder. There are certain side effects associated with paroxetine use that could negatively affect a pilot's performance and become a factor in an aviation accident. Such side effects include nausea, drowsiness, insomnia, and dizziness. It has also been suggested that paroxetine use may increase suicidal behavior and suicidal ideation.

When relying on postmortem specimens for interpretive value, a general understanding of drug distribution throughout postmortem fluids and tissues is important. Utilizing an n-butyl chloride liquid/liquid extraction followed by gas chromatograph/mass spectrometer (GC/MS) analysis with selected ion monitoring, our laboratory developed a method for the identification, characterization, and quantitation of paroxetine. The linear dynamic range was determined to be 3.13 – 1600 ng/mL in blood. Our laboratory then determined the postmortem concentrations of paroxetine in various postmortem tissues and fluids obtained from nine fatal aviation accident cases.

The typical specimen types analyzed for each case included blood, urine, vitreous humor, liver, lung, kidney, spleen, muscle, brain, heart, and bile. Blood paroxetine concentrations obtained from these cases ranged from 0.019 to 0.865 µg/mL. The distribution of paroxetine, expressed as mean specimen/blood ratio, was: 1.67 ± 1.16 urine (n=4), 0.08 ± 0.04 vitreous humor (n=6), 5.77 ± 1.37 liver (n=8), 9.66 ± 2.58 lung (n=9), 1.44 ± 0.57 kidney (n=8), 3.80 ± 0.69 spleen (n=8), 0.15 ± 0.04 muscle (n=8), 4.27 ± 2.64 brain (n=7), and 1.05 ± 0.43 heart (n=8).

The results from this study show that paroxetine is readily distributed to tissues and fluids in the body. The large standard deviations associated with the paroxetine distribution coefficients suggest that paroxetine likely can experience significant postmortem concentration changes.

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INTRODUCTION

The Federal Aviation Administration's (FAA's) Civil Aerospace Medical Institute (CAMI) is responsible under Department of Transportation Orders 8020.11B and 1100.2C to "conduct toxicological analysis on specimens from … aircraft accident fatalities" and "investigate … general aviation and air carrier accidents and search for biomedical and clinical causes of the accidents, including evidence of … chemical (use)." Therefore, following an aviation accident, samples are collected at autopsy and sent to CAMI's Bioaeronautical Sciences Research Laboratory, where toxicological analysis is conducted on various postmortem fluids and tissues. Occasionally, during a toxicological evaluation, potentially impairing compounds are detected in postmortem specimens from aviation accident victims. The laboratory receives blood in approximately 70% of cases received from an aircraft accident; thus, it relies solely on tissues for the remaining cases. Therapeutic levels of a drug are usually only reported in the scientific literature for blood or plasma. However, since blood is not available for all cases sent to CAMI's Toxicology Laboratory, it is necessary to evaluate the distribution of commonly encountered drugs.

Paroxetine, also known as Paxil® (3S,4R-3-[(2H-1,3-benzodioxol-5-yloxy)methyl]-4-(4-flurophenyl)piperidine), is an antidepressant medication used to treat anxiety and depression disorders including major depression, obsessive-compulsive disorder, and post-traumatic stress disorder. It is in the drug class known as selective serotonin reuptake inhibitors (SSRI), along with fluoxetine, citalopram, and sertraline. Paroxetine's central nervous system effects are linked to its ability to block the neuronal reuptake of serotonin. It is a potent reuptake inhibitor of serotonin, with weak reuptake inhibition of norepinephrine and dopamine (1).

Overall, this class of drugs is considered safe, with fewer unwanted side effects than other antidepressant medications. There are, however, adverse effects that have been reported with some SSRIs, including paroxetine, that may affect a pilot's ability to safely operate an aircraft. The possibility of performance-impairing effects such as somnolence, dizziness, and muscular weakness has attracted the attention of the forensic toxicology laboratory at CAMI. Testing for paroxetine in postmortem fluids and tissues is part of routine drug testing for toxicological investigations in pilots involved in aviation accidents.

Typical doses of paroxetine in adults are 20 – 50 mg administered once daily. It is well absorbed, albeit somewhat slowly, from the gastrointestinal tract with approximately 95% protein binding (1,2). Following a single 20 mg oral dose, peak plasma concentrations of paroxetine averaged 11 ng/mL (range, 0.8 – 33 ng/mL) at 3 – 8 h post dose (2). The mean Cmax plasma concentration after the administration of 30 mg/day for 30 days was 61.7 ng/mL, peaking at 5.2 h (1). The half-life of paroxetine was found to range from 12 – 40 h (3).

Paroxetine is extensively metabolized by oxidation, methylation, and conjugation following oral ingestion to inactive metabolites (1,4). Metabolism takes place, in part, by cytochrome P450 2D6 (CYP2D6). This enzyme is readily saturated, even at low doses, resulting in paroxetine's long half-life and the potential for serious drug – drug interactions with pharmaceuticals that are metabolized by CYP2D6. Metabolite I sulfate (17%), metabolite I glucuronide (8%), metabolite II glucuronide (3.1%), parent (0.4%), and trace amounts of other metabolites were found in urine following a single 30-mg paroxetine dose (5).

Postmortem drug concentrations reported in the scientific literature are often from cases involving lethal doses. A few previously published reports showed significantly high paroxetine concentrations in cases where paroxetine was considered a contributor to death (4,6,7). Paroxetine was included in a project carried out at CAMI to describe the involvement of SSRIs in pilot fatalities over an 11-year period (1990 – 2001) (8). These studies were limited, however, in the number of specimen types examined.

The current research adds to those data with a more comprehensive array of findings from multiple postmortem specimen types. A novel analytical method was developed to evaluate the presence of paroxetine in blood, vitreous, liver, lung, kidney, spleen, muscle, brain, and heart. The resulting data further characterize the postmortem distribution of paroxetine for the purpose of assisting forensic toxicologists with interpreting cases involving this drug. A unique part of this work is that the cause of death for these pilots was not drug toxicity. Most distribution studies are not done for cases involving therapeutic concentrations of paroxetine, but are conducted on drug-overdose victims. This research, therefore, shows the distribution data in cases where paroxetine was not believed to be a contributor to death.

MATERIALS AND METHODS

Chemicals and Reagents

All aqueous solutions were prepared using double deionized water (DDW), which was obtained using a Milli-QT_{plus} Ultra-Pure Reagent Water System (Millipore®, Continental Water Systems, El Paso, TX). All chemicals described below were purchased in the highest possible purity and used without any further purification. Paroxetine and d_6-paroxetine were purchased from Cerilliant (Cerilliant Corp., Round Rock, TX) as methanolic standards at a concentration of 1 mg/mL in sealed glass ampoules. The derivatization reagent, pentafluoropropionic anhydride (PFPA), was obtained from Pierce (Pierce Inc., Rockford, IL). Ammonium hydroxide, ethyl acetate, HCl, n-butylchloride (1-chlorobutane), chloroform, and sodium fluoride

were purchased from Fisher Scientific (Pittsburgh, PA). The pH of all solutions was measured using a Corning model 430 pH meter (Corning Life Sciences, Acton, MA) connected to a Corning 3-in-1 model pH electrode.

Gas Chromatographic/Mass Spectroscopic Conditions

All analyses were performed using a bench-top gas chromatograph/mass spectrometer (GC/MS), which consisted of a Hewlett Packard (HP) 6890 series GC, interfaced with a HP 5973 quadrupole MS (Agilent, Palo Alto, CA). The GC/MS was operated with a transfer line temperature of 280°C and a source temperature of 250°C. The MS was tuned on a daily basis using perfluorotributylamine. The electron multiplier voltage was set at 106 eV above the tune value. Chromatographic separation was achieved using a Varian FactorFour® crosslinked 100% methyl siloxane capillary column 12 m x 0.2 mm i.d., 0.33 µm film thickness (Varian Co., Harbor City, CA). Helium was employed as the carrier gas and used at a flow rate of 1.0 mL/min. An HP 6890 autosampler was used to inject 1 µL of extract into the GC/MS. The GC was equipped with a split/splitless injection port operated at 250°C in the splitless mode with the purge time of 0.5 min. The oven temperature profile was established as follows: 130°C – 220°C at 30°C/min, 220°C – 290°C at 35°C/min and a final hold time of 2 min, resulting in a total run time of 6.2 min. Derivatization of paroxetine and d_6-paroxetine with PFPA was performed because the compounds contained a polar functional group that could be replaced to produce a less polar compound with higher mass ions for GC/MS analysis. Initially, standards of each compound (1 µL of a 100 ng/µL solution) were injected individually and analyzed using the full scan mode of the GC/MS, which scanned from 50 to 600 AMU.

Quantitation (quant) and qualifier (qual) ions for each analyte were then selected based on both abundance and mass-to-charge ratio (*m/z*). To increase reproducibility and reduce interference, high mass ions were selected when possible. The ions chosen were as follows: paroxetine: 475.2 (quant), 338.1 and 216.0 (qual); d_6-paroxetine: 481.2 (quant), 344.1 and 222 (qual), and are depicted in Table 1. Upon selection of these unique ions, the MS was run in selected ion monitoring (SIM) mode with a dwell time of 30 msec for each recorded ion.

Acceptability criteria employed for analyte identification and quantitation were as follows: (1) ion ratios for a given analyte, measured as the peak area of a qualifier ion divided by the peak area of the quantitation ion, were required to be within ± 20% of the average of the ion ratios for each respective calibrator used to construct the calibration curve for that analyte; (2) each ion monitored was required to have a minimum signal-to-noise ratio (S/N) of 10; and (3) the analyte was required to have a retention time within ± 2% of the average retention time for each respective calibrator used to construct the calibration curve for that analyte. Analytes not meeting these criteria were reported as either negative or inconclusive.

Sample Selection and Storage

A search of the CAMI toxicology database identified nine paroxetine-positive fatalities from separate civil aviation accidents that had a majority of the desired biological tissues and fluids (blood, urine, vitreous humor, bile, liver, kidney, muscle, lung, spleen, heart, and brain) available for analysis. The cases in this study were from aviation accidents that occurred during a 5-year period ranging from 2002 – 2006. In all cases, blood was stored at -20°C in tubes containing 1% (w/v) sodium fluoride/potassium oxalate until analysis. All other specimens were stored without preservation at -20°C prior to analysis. Blood paroxetine concentrations determined in this study were in agreement with those previously determined by our laboratory via this analytical method.

Calibrator and Control Preparation

A calibration curve was prepared by serial dilution utilizing bovine whole blood as the diluent. Calibrators were prepared from one set of original stock standard solutions, while controls were prepared in a similar manner as calibrators, using bovine whole blood as the diluent, but from a second set of unique stock solutions. Calibration curves were prepared at concentrations ranging from 1.56 – 1600 ng/mL. A minimum of 6 calibrators were used to construct each calibration curve. Controls were prepared at concentrations of 20 and 600 ng/mL and extracted with each batch of unknowns to verify the accuracy of the calibration curve.

Quantitation was achieved via an internal standard calibration procedure. Response ratios for each compound were determined for every sample analyzed. The response ratio was calculated by dividing the area of the analyte peak by the area of the internal standard peak. Calibration curves were derived by plotting a linear regression of the analyte/internal standard response ratio versus the analyte concentration for each respective calibrator. These calibration curves were then used to determine the concentrations of each compound in the prepared controls and biological specimens by comparison of the unknown response ratio to the calibration curve.

Sample Preparation and Extraction Procedure

Postmortem specimens, calibrators, and controls were extracted in the following manner. Tissue specimens were homogenized using an Omni post-mounted homogenizer (Omni Int., Marietta, GA). The generator used with this homogenizer was 30 mm in diameter and set to rotate at 22,000 rpm. Tissues were

Table 1. Retention times and mass fragments for paroxetine and d_6-paroxetine.

Analyte	Retention Time (min)	Quantitation Ions (m/z)	Qualifier Ions (m/z)
Paroxetine-PFPA	4.18	475.2	338.1, 216.0
d_6-Paroxetine-PFPA	4.17	481.2	344.1, 222.0

homogenized following a 1:2 dilution with 1% NaF in DDW. Three mL aliquots of postmortem fluid, calibrator, and control, and 3-g aliquots of each tissue homogenate (1 g tissue) were transferred to individual 16 x 150 mm screw-top tubes. To each specimen, calibrator, and control, 400 ng d_6-paroxetine (1 mL aqueous internal standard) was added. Samples were vortexed briefly and allowed to stand at room temperature for 10 min. Four drops ammonium hydroxide was added to each sample, samples vortexed, and 10 mL n-butylchloride was added. The mixture was then placed on a rotary mixing wheel and mixed for 5 min by simple rotation of the wheel at 15 rpm, followed by centrifugation at 820×*g* for 5 min. Following centrifugation, the organic layer of each sample was transferred to a clean 16 x 125 mm culture tube. Five mL of 1.0 N HCl was added to each sample, samples were mixed for 5 min, and centrifuged at 820×*g* for 5 min. The upper organic phase was then aspirated and 1 mL of concentrated NH_4OH was added to each aqueous extract. Four mL of chloroform was then added, and the samples were rotated for 5 min. The upper aqueous phase was aspirated and the organic phase was dried by adding a small amount (~500 mg) of Na_2SO_4. The organic layer was then transferred to a clean vial, bubbled with HCl vapor, and evaporated in a TurboVap® Concentration Workstation at 40°C (Caliper Life Sciences, Hopkinton, MA) under a stream of nitrogen to dryness. Derivatization was accomplished by adding 50 µL of ethyl acetate, followed by 50 µL of PFPA to each specimen. The samples were then capped tightly, vortexed, and incubated at 70°C for 20 min. Following derivatization, the tubes were allowed to cool to room temperature, and the contents were evaporated to dryness in a TurboVap set at 40°C. Once dry, the contents of each tube were reconstituted in 50 µL of ethyl acetate and transferred to GC/MS vials for analysis.

Extraction Efficiency

We have previously reported a method for the determination of analyte recovery (9). Briefly described, 2 groups of controls, X and Y, prepared using negative whole blood, were extracted in the same manner as described above. Group X was spiked with a precisely known concentration of paroxetine prior to SPE extraction, while group Y was spiked with the same precisely known concentration of paroxetine following SPE extraction. Upon analysis, the average response factor obtained from group X was divided by the average response factor obtained from group Y to yield the percent recovery value (100 * (X/Y) = % recovery) for paroxetine.

RESULTS AND DISCUSSION

Analysis of Paroxetine

The procedure described herein, which utilized liquid/liquid extraction and GC/MS, proved to be a rapid, precise, and sensitive method for the analysis of paroxetine. Paroxetine and d_6-paroxetine provided quantitative and qualitative ions with unique *m/z* and suffered no interference from endogenous/exogenous matrix components.

The linear dynamic range (LDR) and limit of quantitation (LOQ) for paroxetine was determined using bovine whole blood as the matrix. The LDR was determined to be 3.13 – 1600 ng/mL with a correlation coefficient ≥ 0.99 (Table 2). The LDR is broad enough to include not only the known therapeutic concentration range for paroxetine, but also account for sub-therapeutic values and overdose concentrations. The LOQ, defined as the lowest detectable analyte concentration that meets all identification criteria (as discussed in Methods and Materials) and is within 20% of its target concentration, was determined to be 3.13 ng/mL. The LOD was administratively set at the LOQ.

Analyte carryover was not found to be an issue with GC/MS; however, it was initially investigated and subsequently monitored by the use of ethyl acetate blank injections. The injection of an ethyl acetate blank following the 1600 ng/mL blood calibrator showed no carryover contamination. Subsequently, an ethyl acetate blank was utilized between each postmortem specimen throughout the sample sequence to ensure that no carryover from sample to sample had occurred. Additionally, multiple solvent washes of the injector syringe was carried out prior to and after injection of the sample onto the GC/MS. Any specimen concentration found to be greater than the highest calibrator was diluted and re-extracted.

The extraction efficiency for paroxetine utilizing our liquid/liquid procedure fell short of our initial expectations, considering our very low LOD. As can be seen in Table 2, the average recovery of paroxetine at a concentration of 20 ng/mL was 55 ± 2%. The average recovery at a concentration of 600 ng/mL was 58 ± 2%. However, since we were able to achieve a very low LOD with this simple extraction procedure, no further measures were taken to improve the extraction efficiency.

Intra-day (within day) and inter-day (between days) accuracy and precision were examined for this extraction. "Accuracy" was measured as the percent relative error between the experimentally determined and prepared concentrations of a sample. "Precision" was measured as the relative standard deviation (RSD) for

Table 2. LDR, LOD, LOQ and recovery for paroxetine.

Compound	LDR (ng/mL)	LOD (ng/mL)	LOQ (ng/mL)	Extraction Efficiency (%) ± sd*	
				20 ng/mL	600 ng/mL
Paroxetine	3.13-1600	3.13	3.13	55 ± 2	58 ± 2

* n=5

the experimentally determined concentrations. Accuracy and precision studies were performed using whole blood controls at concentrations of 20 and 600 ng/mL. These controls were prepared in 500 mL pools on Day 1 and stored in a refrigerator at 4°C until extracted.

For intra-day analyses, a calibration curve was extracted along with 5 replicates of each control concentration on Day 1 of the experiment. Intra-day relative errors in the 20 ng/mL and 600 ng/mL control groups were ≤ 7%. Furthermore, the intra-day RSD was ≤ 2% for both the 20 ng/mL and 600 ng/mL controls. Intra-day results are summarized in Table 3.

Inter-day accuracy and precision were evaluated by extracting 5 replicates of each of the two control concentrations on Days 2 and 8. The quantitation of paroxetine was based on the calibration curve originally prepared on Day 1. The relative error of the Day 2 control at both concentrations did not exceed 9% and the RSDs were ≤ 3%. The Day 8 controls show a marked decrease in concentration. The 20 ng/mL control showed 16.9 ± 0.3 ng/mL (-16% relative error), while the 600 ng/mL was found to be 499 ± 43 ng/mL (-17% relative error). This decrease in concentration could be paroxetine degradation when stored at 4°C, but is most likely the unsuitability of using a historical calibration curve. As good laboratory practice, and to ensure the highest quality analytical data, we recommend that biological specimens be analyzed promptly after thawing using fresh calibrators.

The long-term stability of paroxetine in whole blood at -20°C was evaluated by monitoring our quality control samples. For quality control purposes, large batches of control material are prepared in blood, urine, or serum at known concentrations, aliquoted into glass screw cap test tubes, and stored at -20°C until needed. Such quality control material is used each time a particular drug is analyzed. A paroxetine quality control, prepared in bovine blood at a target concentration of 190 ng/mL and stored at -20°C until analysis, has been used successfully for 6 years with a mean concentration of 191 ± 14 ng/mL (range 181 – 216 ng/mL, n=6).

Postmortem Concentrations of Paroxetine

As previously mentioned, specimens from fatal aviation accident victims are routinely sent to CAMI for toxicological analysis. Nine separate aviation fatalities (years: 2002 – 2006; ages: 26 – 75, median: 51; gender: male) that had previously screened positive for paroxetine were confirmed and quantitated for paroxetine using the current method. The specimens examined from each victim, if available, included: blood, urine, vitreous humor, muscle, liver, kidney, lung, spleen, brain, and heart. The analytical results for each case may be found in Table 4.

Table 3. Intra- and inter-day accuracy and precision.

		Day 1			Day 2			Day 8		
	Target (ng/mL)	Mean (ng/mL)	CV	%E	Mean (ng/mL)	CV	%E	Mean (ng/mL)	CV	%E
Paroxetine	20	19.1 ± 0.4	2	-4	19.5 ± 0.2	3	-3	16.9 ± 0.3	2	-16
	600	561 ± 8	1	-7	548 ± 14	3	-9	499 ± 43	9	-17

n=5 for all measurements
Accuracy measured as relative error (%E) from target concentration.
Precision measured as CV in replicate measurements.

Table 4. Paroxetine concentrations obtained from 9 pilot fatalities.*

Case	Blood	Urine	VH	Liver	Lung	Kidney	Spleen	Muscle	Brain	Heart
1	0.136	—	0.007	0.841	0.884	0.261	0.631	0.019	0.494	0.168
2	0.561	—	—	1.95	6.48	0.467	2.00	0.057	0.917	0.370
3	0.279	0.120	0.019	1.78	1.57	0.531	1.21	0.044	0.967	0.300
4	0.865	—	—	5.19	10.1	1.61	2.29	0.065	—	0.629
5	0.033	0.111	—	0.197	0.325	0.072	0.126	0.005	2.24	0.058
6	0.579	0.447	0.031	2.51	3.97	0.798	2.63	0.123	1.37	0.348
7	0.019	—	0.003	0.103	0.260	0.015	0.055	0.004	0.103	0.031
8	0.047	0.099	0.004	0.395	0.489	—	—	—	—	—
9	0.110	—	0.006	—	1.20	0.070	0.435	0.014	0.355	0.076

* All concentrations shown in units of µg/mL or µg/g
— Specimen type not available for analysis
VH – vitreous humor

Table 5. Postmortem tissue distribution coefficients for paroxetine.

	Urine/ Blood	VH/ Blood	Liver/ Blood	Lung/ Blood	Kidney/ Blood	Spleen/ Blood	Muscle/ Blood	Brain/ Blood	Heart/ Blood
n	4	6	8	9	8	8	8	7	8
Mean	1.67	0.08	5.77	9.66	1.44	3.80	0.15	4.27	1.05
S.D.	1.16	0.04	1.37	2.58	0.57	0.69	0.04	2.64	0.43
CV	70	48	24	27	40	18	31	62	41

VH – vitreous humor
S.D. – standard deviation
CV – coefficient of variation

Therapeutic blood concentrations for paroxetine range from 0.010 to 0.120 μg/mL (10). Toxicity has been reported to start at a concentration of 0.350 μg/mL (10). Lethal levels of paroxetine have been reported at concentrations of 3.7 μg/mL and above (10). Blood concentrations observed in the current study ranged from 0.019 to 0.865 μg/mL. As can be seen in Table 4, 6 of the 9 cases are consistent with therapeutic concentrations. Three fall within the lower toxic range. However, the site from which the blood was collected at autopsy is unknown for each of these cases. In addition, postmortem redistribution (PMR), the movement of drug out of tissue compartments into blood, may have played a role in altering blood paroxetine concentrations after death. The blood concentrations in Table 4, therefore, may not be representative of the levels observed prior to death.

On average, the highest concentrations of paroxetine in each victim were found in lung, liver, and spleen tissue specimens (Table 4). The general trend for highest concentration to lowest concentration of paroxetine was: lung, liver, spleen, brain, blood, urine, heart, vitreous humor, muscle, and kidney. We anticipated paroxetine tissue concentrations to be high, given a 17 L/kg volume of distribution (11).

The distribution coefficients for paroxetine, expressed as non-blood specimen concentration/blood concentration, were found to be: 1.67 ± 1.16 urine, 0.08 ± 0.04 vitreous humor, 5.77 ± 1.37 liver, 9.66 ± 2.58 lung, 1.44 ± 0.57 kidney, 3.80 ± 0.69 spleen, 0.15 ± 0.04 muscle, 4.27 ± 2.64 brain, and 1.05 ± 0.43 heart (Table 5). Paroxetine distribution coefficients obtained in this study had coefficient of variation (CV) values that ranged between 18 and 62% (urine was not included here as it is an excretory fluid).

The large CV's associated with the postmortem distribution coefficients could result from numerous factors, such as differing blood collection sites at autopsy, postmortem interval, PMR, contamination, hydrolysis, bacterial activity, time between oral paroxetine administration and death, paroxetine dosage, age of the victim, diet, and health of the victim (12-16). The blood collection site and postmortem interval for these cases are unknown. However, in most of our cases in which the collection site is noted, the blood typically originates from the chest cavity. Chest cavity blood may be contaminated by the simple diffusion of paroxetine from surrounding drug-rich tissues, e.g., lung. Alkaline compounds, such as paroxetine, readily undergo postmortem redistribution in the interval between death and specimen collection.

CONCLUSION

The CAMI Toxicology Laboratory developed a method for the identification, characterization, and quantitation of paroxetine that is rapid, reliable, and extremely sensitive. By utilizing liquid/liquid extraction, we achieved a clean extract that required minimal analyst time and low solvent volumes. This analytical method achieved acceptable extraction efficiency and a limit of detection and quantitation of 3.13 ng/mL. Paroxetine concentrations in the nine aviation fatalities we tested ranged from lower therapeutic to high therapeutic/ lower toxic range. The results from this study show that paroxetine is readily distributed to tissues and fluids in the body, with the highest concentration being found in lung. By and large, the coefficient of variation's calculated for the paroxetine distribution coefficients were extraordinarily large, suggesting that paroxetine can experience significant postmortem concentration changes and renders postmortem drug concentrations that are difficult to interpret.

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