The LC/MS Quantitation of Vardenafil (Levitra®) in Postmortem Biological Specimens

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During the investigation of aviation accidents, postmortem specimens from accident victims are submitted to the Federal Aviation Administration’s Civil Aerospace Medical Institute (CAMI) for toxicological analysis. As new medications are introduced to the market and are subsequently used by aviation accident victims, CAMI’s forensic toxicology laboratory is tasked with developing analytical methods for the determination of these compounds. This report presents a rapid and reliable method for the identification and quantitation of vardenafil (Levitra®) in biological specimens. This procedure utilizes sildenafil-d₈, which structurally is closely related to vardenafil, as an internal standard for more accurate and reliable quantitation. The method incorporates solid phase extraction and LC/MS/MS and MS/MS/MS utilizing an atmospheric pressure chemical ionization ion trap mass spectrometer in the positive chemical ionization mode. Solid-phase extraction proved to be exceptionally efficient providing recoveries that ranged from 94-97%. The limit of detection for vardenafil was determined to be 0.19 ng/mL. The linear dynamic range for this compound was 0.39 – 200 ng/mL. This method was successfully applied to postmortem fluid and tissue specimens obtained from an aviation accident victim. This novel analytical procedure proved to be simple, accurate, and robust for the identification and quantitation of vardenafil in postmortem specimens.
INTRODUCTION

The Federal Aviation Administration’s Civil Aerospace Medical Institute (CAMI) is responsible under U.S. 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 Forensic Toxicology Research Laboratory where toxicological analysis is conducted on various postmortem fluids and tissues.

Vardenafil (Levitra®), prescribed as an oral treatment for erectile dysfunction (ED), was introduced to the United States in 2003. Within a year of its introduction vardenafil prescriptions increased approximately 400%, and it is now one of the most widely prescribed treatments for ED.¹ Vardenafil, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl)sulfonyl]-4-ethyl-piperazine, shown in Figure 1, is a selective inhibitor of the cGMP-specific phosphodiesterase type 5 enzyme (PDE5) found predominantly in the penile corpus cavernosum.²⁻⁸

Vardenafil undergoes hepatic metabolism, producing the active desethyl metabolite, M1. M1 contributes to the observed pharmacological effects provided by vardenafil, as M1 exhibits approximately 30% of the potency of the parent drug.¹ Under steady-state conditions, the plasma concentration of M1 is approximately 26% of that seen for Vardenafil.¹ After oral administration of vardenafil, peak plasma concentrations are obtained within 30-60 min.¹ Vardenafil and its active metabolite have a terminal half-life of approximately 4-5 hours.¹

Vardenafil, while relatively safe, has certain side effects that could create aviation safety-related hazards. While vardenafil inhibits PDE5, it also has a high affinity for phosphodiesterase type 6 (PDE6), a retinal enzyme involved in phototransduction.¹⁻⁹ The inhibition of PDE6 can result in a condition known as “blue tinge,” the inability to discriminate between blue and green colors.¹⁰ This “blue tinge” impairment could hinder the execution of certain tasks, such as a pilot relying upon instruments during adverse meteorological conditions and/or night flights.¹¹ Additionally, vardenafil has been shown to potentiate the hypotensive effects of nitrates commonly employed in the treatment of certain heart conditions.¹²

Due to its increasing popularity, the presence of vardenafil in aviation accident victims will become more common. This paper describes a method for the quantitation of vardenafil in postmortem specimens utilizing solid phase extraction (SPE) and liquid chromatography (LC) with atmospheric pressure chemical ionization (APCI) ion trap mass spectrometry (MS). This technology allowed for MS/MS and MS/MS/MS detection in the positive ionization (PCI) mode.

Figure 1. Chemical structures of vardenafil (a) and sildenafil-d₈ (b).
MATERIALS AND METHODS

Reagents, Standards, and Supplies

All aqueous solutions were prepared using double deionized water (DDW), which was obtained using a Milli-Q® Ultra-Pure Reagent Water System (Millipore®, Continental Water Systems, El Paso, TX). All chemicals were purchased in the highest possible purity and used without any further purification. All solvents were of HPLC-grade and were obtained from Fisher Scientific (Fischer Scientific Co., Fair Lawn, NJ). Formic acid (97%) was purchased from ICN (ICN Biomedicals, Inc., Irvine, CA). Vardenafil was obtained from Bayer pharmaceutical corporation (Bayer Corp., West Haven, CT). Sildenafil-d₈ was synthesized by and obtained from SynFine Research Inc. (Ontario, Canada).

Stock standard solutions of vardenafil were prepared at a concentration of 1 mg/mL in methanol. A stock solution of the internal standard, sildenafil-d₈, was prepared at 100 μg/mL in methanol. Fifty mM formic acid constituted the aqueous portion of the HPLC mobile phase and was adjusted to pH 5.00 with conc. ammonium hydroxide. The formic acid buffer was mixed with acetonitrile in a 98:2 (v:v) ratio, respectively, to help prevent the growth of microbes. This mixture was filtered through a vacuum filtering apparatus that incorporated a 0.45 μm GH polypropylene membrane filter obtained from Pall Gelman laboratory (Pall Corp., East Hills, NY). The primary organic component of the mobile phase was HPLC grade acetonitrile, which was filtered prior to use through a vacuum filter apparatus that incorporated the same type of membrane filter described above.

Instrumentation

Analyte separation was achieved using a Hewlett-Packard 1100 HPLC (Hewlett Packard Co., Wilmington, DE) equipped with a Security Guard™ C-8 guard column (4.0 x 3.0 mm i.d., 3 μm particles) from Phenomenex® (Torrance, CA), followed immediately by an Atlantis™ LC-18 (150 x 4.6 mm i.d., 3 μm particles) analytical column obtained from the Waters Corporation (Milford, MA). Samples were injected using a Hewlett Packard G1313A autosampler (Hewlett Packard Co., Wilmington, DE). Identification and quantitation were accomplished using a Thermo Finnigan model LCQ atmospheric pressure chemical ionization (APCI) ion trap mass spectrometer (Thermo Finnigan Corp., San Jose, CA), which utilized nitrogen as the sheath gas and helium as the reagent gas. Control of the HPLC system, integration of the chromatographic peaks, and communication with the mass spectrometer were accomplished using a Gateway 2000 E-4600-SE personal computer using Xcalibur™ LC/MS software (Thermo Finnigan Corp., San Jose, CA).

LC/MS/MS and MS/MS/MS Method

For all determinations, the HPLC was operated in an isocratic mode with a flow rate of 1.00 mL/min. The mobile phase ratio employed was 70:30 (acetonitrile:buffer). The sample injection volume was held constant at 10 μL. The HPLC column was routinely equilibrated overnight prior to use. Following use, the column was washed with and stored in 50:50, acetonitrile:H₂O. Working with neat standards of vardenafil and sildenafil-d₈, the initial investigation began by observing the response received from these 2 compounds when injected directly into the LCQ. Initial ionization evaluation of these compounds indicated that positive chemical ionization (PCI), creating [M+H]+ ions, was much more effective than negative chemical ionization (NCI), which formed [M-H]- ions. Initially, APCI-PCI-MS [M+H]+ parent ions were identified for both compounds by infusing the desired compound at a concentration of approximately 10 μg/mL, prepared by dilution from the stock solutions using acetonitrile, into the LCQ at a constant rate of 25 μL/min. Following [M+H]+ ion identification, ionization conditions were optimized by infusing each analyte directly into the mobile phase, which was then introduced into the mass spectrometer at a flow rate of 1.00 mL/min. Tuning the MS for the desired ions was then accomplished using the autotune feature of the Xcalibur™ software. Each sample analysis consisted of 1 data collection segment. This segment collected data for both vardenafil and the internal standard sildenafil-d₈.

The operating conditions for the data collection segment were as follows: APCI capillary temperature, 150°C; APCI vaporizer temperature, 450°C; source voltage, 5.00 kV; source current, 5.00 µA; sheath gas flow (nitrogen), 80.0; auxiliary gas flow (nitrogen), 10.0; capillary voltage, 23.0 V; tube lens offset, 35.0 V; octapole 1 offset, -1.75 V; octapole 2 offset, -6.00 V; interoctapole lens voltage, -18.00 V; trap DC offset voltage, -15 V; multiplier voltage, 0.0 V; and 1 micro-scan having a maximum ion injection time of 200 msec. This segment was further split into 3 separate scan events. Scan event 1 collected the sildenafil-d₈ and vardenafil parent, [M+H]+ ions at m/z 483.3 and m/z 489.4, respectively. Scan event 2 collected the vardenafil daughter ions at m/z 376.0 and 376.1 following collision-induced dissociation (CID) of the parent ion (m/z 489.4) using a collision energy of 46%. Scan event 3 collected the vardenafil granddaughter ion at m/z 284.1 following CID of the daughter ion (m/z 376.0) using a collision energy of 42%.
Full scan spectra for vardenafil provided “fingerprints” used for analyte identification and confirmation. These spectra are shown in Figures 2 through 5. Ions having the highest abundance in the MS/MS mode were used for quantitation of vardenafil. The MS/MS spectra of vardenafil shows two predominant ions as can be seen in Figure 4. These ions, at \( m/z \) 376.0 and \( m/z \) 377.1, were summed for the quantitation of this compound. The molecular ion of the internal standard, sildenafil-\(d_8\), at \( m/z \) 483.3 was utilized for quantitation. The MS/MS/MS full spectrum was used for vardenafil confirmation.

**Calibrators and Controls**

Calibration curves were prepared by serial dilution utilizing bovine whole blood as the diluent. Calibrators were prepared from one original stock standard solution of vardenafil. Controls were prepared in a similar manner as calibrators, using the same bovine whole blood as diluent but employing a second original stock solution. Calibration curves were routinely prepared at a concentration range of 0.39 – 200 ng/mL. A minimum of 7 calibrators was used to construct each calibration curve. Controls used for the determination of accuracy, precision, and compound stability were prepared at 2, 20, and 200 ng/mL. Controls were prepared in pools large enough to provide samples for the entire study. A sildenafil-\(d_8\) working standard was prepared at a final concentration of 50 ng/mL by dilution with DDW from the stock solution.

Quantitation of vardenafil in biological specimens was achieved via an internal standard calibration procedure. Response factors for vardenafil were determined for each sample. The response factor was calculated by dividing the area of the analyte peak by the area of the internal standard peak. Calibration curves were prepared by plotting a linear regression of the analyte/internal standard response factor versus the analyte concentration for the calibrators and were used to determine the concentrations of vardenafil in controls and specimens.

**Sample Extraction**

Calibrators, controls, and postmortem specimens were prepared and extracted in the following manner. Tissue specimens were homogenized using a PRO250 post-mounted homogenizer (PRO Scientific, Oxford, CT) employing a 30.0 mm saw-toothed generator set to rotate at 22,000 RPM following a 2:1 dilution with 1.00% sodium fluoride (2 g 1.00% NaF:1 g wet tissue). Three mL aliquots of calibrators, controls, and postmortem fluids and 3 g aliquots of tissue homogenate (1 g tissue)
Figure 3. MS spectrum of vardenafil (m/z 489.4).

Figure 4. MS/MS spectrum of vardenafil (m/z 489.4 → spectrum).
were transferred to individual 15 mL screw-top vials. To each sample, 50 ng of internal standard was added (1.00 mL of the 50 ng/mL stock solution). The samples were vortexed and allowed to stand for 10 min. Nine mL iced-cold acetonitrile was added to each sample. The mixture was then placed on a rotary mixing wheel and mixed for 15 min by simple rotation of the wheel at 15 rpm. Centrifugation at $820 \times g$ for 5 min provided removal of cellular debris and proteins. Following centrifugation, the supernatant was transferred to clean 15 x 125 mm culture tubes and evaporated in a TurboVap® water evaporator at 40°C (Caliper Life Sciences, Hopkinton, MA) under a stream of dry nitrogen to a volume less than 1 mL. Following acetonitrile evaporation, 4.00 mL 0.10 M phosphate buffer, pH 6.00 was added to each sample. The extracts were transferred to solid phase extraction (SPE) columns, which had been pre-conditioned with 2.00 mL methanol, followed by 2.00 mL 0.10 M phosphate buffer, pH 6.00. Care was taken not to dry the SPE column prior to extract addition. The Bond Elute Certify® SPE columns employed for this study were obtained from Varian (Varian Co., Harbor City, CA). Column flow rates of 1 – 2 mL/min were maintained in each step using a Varian 24 port Cerex® SPE processor (Varian Co., Harbor City, CA) with a nitrogen pressure of 3 psi. Once each sample had passed through its respective column, the columns were washed with 1.00 mL of 1.0 M acetic acid and then dried completely with 25 psi nitrogen for 5 min. The columns were then washed by adding 6.00 mL methanol and were again dried completely with 25 psi nitrogen for 5 min. The analytes were eluted from the columns with 3.00 mL of 2% ammonium hydroxide in ethyl acetate, which was prepared fresh daily. Eluents were evaporated to dryness in a water bath at 40°C under a stream of dry nitrogen, reconstituted in 50.0 μL acetonitrile, and transferred to LC sample vials for analysis. All specimens were analyzed at one time to avoid inter-assay variations. Specimens with analyte concentrations above the associated calibration curves were diluted by an appropriate factor and re-extracted. When specimen dilution was necessary, a control was diluted by the same factor to ensure dilution accuracy.

**Recovery**

The recovery of each analyte was determined using the following procedure.13 Two groups, X and Y, of controls prepared using negative whole blood diluent were extracted in the same manner as described immediately above. Group X was spiked with a precisely known amount of vardenafil prior to extraction, and group Y was spiked with the same precisely known amount of vardenafil fol-

![Figure 5. MS/MS/MS spectrum of vardenafil (m/z 489.4 → 376.0 → spectrum).](image-url)
lowing solid phase 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 \((100 \times \frac{X}{Y} = \% \text{ recovery})\) for each of the compounds.

**RESULTS AND DISCUSSION**

**Method Validation**

The procedure described herein provides a rapid, reproducible, and accurate method for the determination of vardenafil in postmortem specimens. This procedure incorporates SPE and LC/MS/MS/MS utilizing an APCI ion trap MS in the PCI mode. The use of SPE provided a cleaner extract and required less organic solvent than did an alternative liquid-liquid extraction procedure.

By incorporating APCI-MS in the PCI mode, MS spectra were produced consisting predominantly of the protonated \([M+H]^+\) ion. By utilizing an ion trap MS, we were able to conduct MS/MS on these unique ions. The vardenafil \([M+H]^+\) ion used to create the MS/MS spectra was found at \(m/z\) 489.4. MS/MS/MS spectra were then obtained by conducting MS on the vardenafil MS/MS daughter ion at \(m/z\) 376.0.

The vardenafil chromatographic peak experienced no interference from endogenous sample matrix components. Matrix interference was monitored by the use of whole-blood negative controls that were spiked only with sildenafil-\(d_8\) prior to extraction. Both vardenafil and sildenafil-\(d_8\) were eluted from the analytical column in less than 4 min. Figure 6 shows a representative LC/MS chromatogram. LC retention times were used as one analyte acceptability criteria. Vardenafil retention times obtained from postmortem specimens were required to be within \(\pm 2.0\%\) of the average calibrator retention time. Typical retention times were 2.41 and 2.54 min for vardenafil and sildenafil-\(d_8\), respectively.
Quantitation was accomplished by collecting the highest abundance ion in the MS/MS mode. With vardenafil having two predominant ions with nearly equal abundance in the MS/MS mode, the abundance obtained for each of these ions was summed for quantitative purposes. The total area of the two predominant MS/MS ions for vardenafil divided by the area of the molecular ion of the internal standard, sildenafil-\(d_9\), resulted in a response factor that was used for quantitation. The linear dynamic range (LDR), limit of detection (LOD), and limit of quantitation (LOQ) were determined by analysis of a calibration curve that contained calibrators ranging in concentration from 0.10 – 6400 ng/mL. The LDR for vardenafil was determined following this analysis and found to be 0.39 – 200 ng/mL. The correlation coefficient for this calibration curve exceeded 0.992 when a weighting factor of 1/X was used. For vardenafil, non-linearity was observed at concentrations greater than 200 ng/mL. The LOD and LOQ determined for vardenafil are listed in Table 1. The LOD was defined as the lowest concentration of analyte having a minimum signal-to-noise ratio (S/N) of 5, in addition to meeting the MS/MS and MS/MS/MS spectral “fingerprint” identification and retention time criteria. The LOQ was defined as meeting all LOD criteria, plus having a S/N of 10, and an experimentally determined value within ±20% of its prepared concentration. The LOD and LOQ for vardenafil when extracted from whole blood were determined to be 0.19 ng/mL and 0.39 ng/mL, respectively.

Instrumental carryover from one sample to the next was not found to be a problem. It was, however, initially investigated and subsequently monitored by the use of acetonitrile solvent blank injections. An acetonitrile blank, injected following the highest calibrator, showed no carryover contamination. Subsequently, blanks were used following each postmortem specimen in the sample sequence to verify that no sample-to-sample contamination occurred.

The vardenafil extraction efficiency at various concentrations obtained from this SPE procedure was exceptional. As can be seen in Table 1, the average recovery of vardenafil at a concentration of 2 ng/mL was 95 ± 7%. The average recovery of vardenafil at a concentration of 20 ng/mL was 98 ± 6%, and the average recovery of vardenafil at a concentration of 200 ng/mL was 94 ± 4%.

Intra-day (within day) and inter-day (between days) accuracy and precision were examined for this extraction procedure. 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 the experimentally determined concentrations. Accuracy and precision studies were performed using whole blood controls at concentrations of 2, 20, and 200 ng/mL. These values were chosen because they are distributed throughout the extensive LDR of this compound. These controls were prepared in 500 mL quantities on Day 1 of the experiment and stored 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 2, 20, and 200 ng/mL control groups were ≤ 3% for this analyte. Furthermore, the intra-day RSD was ≤ 2% at each vardenafil control concentration. Intra-day results are summarized in Table 2.

Inter-day accuracy and precision were evaluated by extracting 5 replicates of each of the three control concentrations on Days 2, 4, and 7 and generating quantitative values by utilizing the calibration curve originally prepared on Day 1. The inter-day relative errors for this analyte at each control concentration did not exceed 9%. The RSD for the 2 ng/mL vardenafil control was ≤ 3% over Days 2, 4, and 7. Both the 20 and 200 ng/mL controls had RSD values ≤ 4% over the same time period. These inter-day results show that this method is both accurate and precise over a 7-day period (Table 2).

The stability of vardenafil in whole blood was evaluated by examining the control concentrations obtained on Day 7 of the inter-day experiment (Table 2). Vardenafil showed no apparent decrease in concentration after 1 week of storage at 4°C at concentrations of 2 and 20 ng/mL. The 200 ng/mL control showed a slight decrease in concentration over this time period. These results demonstrate that whole blood specimens may be stable for 7 days when stored at 4°C. However, as good laboratory practice and to ensure the highest quality analytical

<table>
<thead>
<tr>
<th>Compound</th>
<th>LDR (ng/mL)</th>
<th>LOD (ng/mL)</th>
<th>LOQ (ng/mL)</th>
<th>Recovery (%) 2 ng/mL</th>
<th>Recovery (%) 20 ng/mL</th>
<th>Recovery (%) 200 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vardenafil</td>
<td>0.39 – 200</td>
<td>0.19</td>
<td>0.39</td>
<td>95 ± 7</td>
<td>98</td>
<td>94 ± 4</td>
</tr>
</tbody>
</table>

* n = 5 at each recovery concentration.
data, we recommend that biological specimens always be analyzed promptly after thawing.

Postmortem Specimen Analysis

In fatal aviation accidents, specimens from accident victims are routinely sent to the Federal Aviation Administration’s Civil Aerospace Medical Institute for toxicological analysis. Postmortem fluid and tissue samples obtained from one such victim were examined for vardenafil using the current method. This case was specifically selected because evidence obtained from the scene of the accident suggested that the accident victim had been prescribed Levitra®. The fluid and tissue specimens examined from this case included blood, bile, liver, kidney, heart muscle, lung, and skeletal muscle. The quantitative results of this analysis are presented in Table 3.

As previously stated, sildenafil-d₈ was used as the internal standard in this study as an alternative to deuterated vardenafil which is not commercially available. These analogs are structurally nearly identical; however, the interpretation of quantitative data for vardenafil obtained from specimen types other than blood should be closely scrutinized due to possible variations in extraction efficiency between specimen types.

Each specimen type analyzed in this case was found positive for vardenafil. The concentration of vardenafil in the blood was found to be 291 ng/mL. The vardenafil concentration in bile was 1665 ng/mL. The liver concentration was 86 ng/g, while kidney was 15 ng/g. The skeletal muscle was found to contain vardenafil at 8 ng/g, while the heart had 26 ng/g. Lung tissue was also analyzed in this case and was found to contain vardenafil at 234 ng/g.

<table>
<thead>
<tr>
<th>Target Conc. (ng/mL)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD (ng/mL)</td>
<td>Mean</td>
<td>SD (ng/mL)</td>
</tr>
<tr>
<td></td>
<td>2.05</td>
<td>0.02</td>
<td>2.03</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>+3%</td>
<td>1%</td>
<td>+2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* n = 5 at each concentration for each day, controls were run on Days 1, 2, 4, and 7.
In this case, the highest concentration of vardenafil was found in bile. This was an expected result, as the major excretion route for this analyte is in the feces. Following bile, the highest concentrations of vardenafil were found in the blood, lung, liver, heart, kidney, and skeletal muscle, respectively. While little to no data exists for tissue concentrations of vardenafil, antemortem plasma values have been reported. Peak plasma concentrations of vardenafil range from 10 – 26 ng/mL following the maximum daily-recommended dose of 20 mg. The blood value determined in the case presented here is significantly higher than what is expected based on the reported concentrations observed following maximum daily recommended dosage. An exceptionally high blood concentration could indicate one or more of the following: an inappropriately high dosage, vardenafil metabolism deficiency, hepatic impairment, or possible drug interaction with erythromycin or ketoconazole. Another possibility for the seemingly high blood value could be postmortem redistribution. The volume of distribution for vardenafil is high at 208 L. This high distribution value suggests the possibility that this compound could easily redistribute between fluids and tissues with high water content after death. An accurate interpretation of the high blood concentration found in this case is difficult due to the lack of published scientific research on this subject and, thus, its significance is not known.

### CONCLUSION

The use of vardenafil for the treatment of erectile dysfunction has increased dramatically over the past 2 years. Thus, the possible occurrence of undesirable side effects is of concern in the aviation safety community. With this in mind, a method for the identification and quantitation of vardenafil has been developed that is rapid, reliable, and sensitive. By utilizing SPE, a clean extract was achieved with minimal solvent use. Additionally, the extraction provided excellent analyte recovery. The method described in this manuscript exemplifies the effectiveness of utilizing LC/MS/MS for the determination of large, nonvolatile and/or thermally labile compounds. APCI-MS in the PCI mode is a “soft” ionization technique that yielded a simple spectrum consisting of a predominant protonated \([\text{M+H}]^+\) ion. The LCQ ion trap enhanced the specificity and sensitivity of the method by allowing for the MS/MS and MS/MS/MS analyses of these unique \([\text{M+H}]^+\) ions. The development of this method sets the stage for continuous evaluation of any adverse effects related to vardenafil in civil aviation community.

### Table 3. Concentrations of vardenafil found in the victim of a fatal aviation accident.*

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Case 1 Vardenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>291</td>
</tr>
<tr>
<td>Bile</td>
<td>1665</td>
</tr>
<tr>
<td>Liver</td>
<td>86</td>
</tr>
<tr>
<td>Kidney</td>
<td>15</td>
</tr>
<tr>
<td>Muscle</td>
<td>8</td>
</tr>
<tr>
<td>Heart</td>
<td>26</td>
</tr>
<tr>
<td>Lung</td>
<td>234</td>
</tr>
</tbody>
</table>

*Concentration units either ng/mL (fluid) or ng/g (tissues).
REFERENCES


