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CASE REPORT

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Postmortem Tissue Distribution of Atomoxetine Following Fatal and Nonfatal Doses—Three Case Reports

ABSTRACT: Atomoxetine (Strattera®, Lilly) is a selective norepinephrine reuptake inhibitor (SNRI) prescribed for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. It is the first nonstimulant drug-therapy option for ADHD. Three case reports are presented in which atomoxetine was detected in two individuals who died from causes unrelated to the drug and a third from the intentional ingestion of atomoxetine and other drugs. In addition, a brief description of the pharmacokinetics and side effects of atomoxetine are given. Postmortem fluid and tissue concentrations of atomoxetine were as follows: aortic blood, <0.1–8.3 mg/L; femoral blood, 0.33–5.4 mg/L; vitreous humor, 0.1–0.96 mg/L; bile, 1.0–33 g/L; urine, <0.1 mg/L; liver, <0.44–29 mg/kg; and gastric contents, 0.0097–16.8 mg total. Autopsy findings in the two cases in which death was not attributed to drug toxicity included arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy. The analytical method utilized was a modified basic drug, liquid–liquid procedure followed by gas chromatography/mass spectrometry and nitrogen phosphorous detection. Atomoxetine can be considered nontoxic at whole blood and liver concentrations below 1.3 mg/L and 5 mg/kg, respectively.

KEYWORDS: forensic science, atomoxetine, postmortem

Atomoxetine (Strattera®, Lilly, Indianapolis, IN) is a selective norepinephrine reuptake inhibitor (SNRI), provided as the hydrochloride salt in the enantiomerically pure *R* (−) isomer form (Fig. 1). Atomoxetine was approved by the Food and Drug Administration (FDA) for use in November 2002 for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. It is the first nonstimulant drug-therapy option for ADHD. The precise mechanism of action of atomoxetine is unclear other than that it increases the concentration of norepinephrine in the brain, a neurotransmitter thought to be important in regulating attention, impulsivity, and activity levels. Off-label uses from anecdotal evidence include depression, panic and anxiety, and bipolar disorder.

Atomoxetine has been shown through clinical trials to be effective in children and adolescents at a starting dose of 0.5 mg/kg/day, increased after a minimum of 3 days to a total dose of 1.2 mg/kg/day up to 100 mg/day, whichever is lowest. In adults, based on an average body weight of 70 kg, an initial daily dose of 40 mg is recommended, increased to 80–100 mg as needed. The drug is provided for oral administration in capsules containing the equivalent of 10, 18, 25, 40, or 60 mg of atomoxetine.

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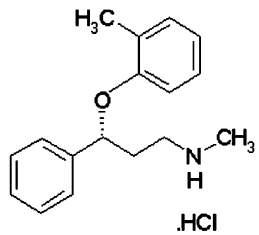
Pharmacokinetics (1)

Atomoxetine is well absorbed after oral administration, which is only minimally retarded by food. It has a bioavailabilty of 63% and is highly plasma protein bound (98% to albumin). Maximal plasma concentrations of atomoxetine occur 1–2 h after dosing, and its half-life is approximately 5 h. Atomoxetine has a low volume of distribution (V_d) (0.85 L/kg) suggesting little tissue sequestration. Atomoxetine is metabolized primarily by cytochrome P450 CYP2D6 to yield 4-hydroxyatomoxetine, which is subsequently glucuronidated. A second metabolite, *N*-desmethylatomoxetine is formed by the action of CYP2C19. A report by Witcher et al. (2) indicates that children and adolescents metabolize atomoxetine rapidly and similarly to adults, suggesting that the isoenzymes mature by age 7. 4-Hydroxyatomoxetine has equipotent SNRI pharmacological activity to the parent drug but is only present in the plasma, under therapeutic dosing conditions, at very low concentrations. *N*-Desmethylatomoxetine not only has less pharmacological activity than atomoxetine, but is also present



(-)-N-methyl-3-phenyl-3-(o-tolyloxy)-propylamine hydrochloride
$C_{17}H_{21}NO.HCl$; Molecular Weight 291.82

FIG. 1—*Atomoxetine hydrochloride.*

TABLE 1—*Pharmacokinetic parameters of atomoxetine.*

Drug *Metabolite*	Elimination Half-Life $t_{1/2}$ (h)	V_d (L/kg)	% Plasma Protein Binding	Therapeutic Plasma Concentration EM (mg/L)*	Therapeutic Plasma Concentration PM (mg/L)*	Isoenzymes Involved in Metabolism
Atomoxetine	5	0.85	98 (albumin)	0.036–0.160	0.500–0.915	CYP2D6
4-Hydroxy-	*6–8*			*0.002*	*Not known*	CYP2C19
N-Desmethyl-	*6–8*			*0.007*	*0.190–0.260*	

All values are subject to interindividual variation.
*Based on 40 mg/day for 5 days administered to adult males between the ages of 19–54 (3).
EM, extensive metabolizers; PM, poor metabolizers.

in plasma at lower concentrations. The elimination half-life of the two metabolites is 6–8 h. Greater than 80% of the dose of atomoxetine is excreted in the urine as 4-hydroxyatomoxetine-*O*-glucuronide, with less than 17% of the dose appearing in the feces. This indicates extensive biotransformation. Poor CYP2D6 metabolizers will display altered pharmacokinetic data. Some pharmacokinetic data are summarized in Table 1.

Side Effects and Drug–Drug Interactions

Typical side effects of atomoxetine are upset stomach, nausea and vomiting, decreased appetite, constipation, headache, dry mouth, urinary hesitance, and insomnia. Atomoxetine may also increase blood pressure and heart rate and should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. Coadministration of atomoxetine with albuterol results in the potentiation of albuterol's effects on increased heart rate and blood pressure and should be closely monitored in those patients. Despite atomoxetine's reliance on CYP450 isoenzymes for its metabolism, it does not appear to either inhibit or induce these enzymes. In addition, atomoxetine did not displace the binding of other highly plasma protein bound drugs such as warfarin, acetylsalicylic acid, or phenytoin, or vice versa, resulting in no pharmacokinetic drug interactions. Atomoxetine, unlike selective serotonin reuptake inhibitors, can be discontinued without being tapered with any ill effects.

Atomoxetine is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or those within 2 weeks of discontinuation of a MAOI. Patients with narrow angle glaucoma should also avoid the use of atomoxetine because it can increase the risk of mydriasis (1).

Toxicity

Little is known through clinical trails or literature reports about the toxicity of atomoxetine in overdose; even less is known about postmortem toxicology. To date, the LA Coroner's Office has reported 2 cases involving atomoxetine (4). The findings were considered incidental to the cause and manner of death.

Three cases involving atomoxetine, 2 considered incidental findings, and the other an intentional overdose, are presented here. The corresponding postmortem fluid and tissue distribution of atomoxetine in addition to significant autopsy findings are reported.

Case Histories

Case 1

An 11-year-old Caucasian female (65 in; 118 lb) collapsed during a ball game at school. Paramedics found her unresponsive with dilated pupils, and despite resuscitation efforts, she failed to regain consciousness. Autopsy findings revealed significant adipose tissue replacement of the myocardium of the right ventricular wall of the heart. The right ventricle was also dilated and there was a pericardial effusion, indicative of heart failure. The deceased was a cheerleader and exercised vigorously. A few hours prior to her collapse, she complained to her teacher that she was "not feeling well." Her parents stated that she had seemed "withdrawn for a couple of weeks." In addition, she had been diagnosed with ADHD for which she was originally prescribed Adderall® (Shire U.S. Inc., Newport, KY) (dextroamphetamine). Several weeks prior to her death, the deceased was started on atomoxetine while continuing treatment with dextroamphetamine. The cause of death was ruled arrhythmogenic right ventricular dysplasia, and the manner natural.

Case 2

A 19-year-old Caucasian female (64 in; 118 lb) with a 3-year history of depression and previous suicide attempts was found at home, groggy with poor respiration. A suicide note was found at the scene with empty pill bottles for the prescribed medication, which is listed below. Resuscitation attempts failed and the deceased was pronounced dead in the intensive care unit 2 h later. Autopsy findings included pill fragments within the gastric contents, and congestion of the lungs. The decedent had been prescribed Effexor® (Wyeth, Philadelphia, PA) (venlafaxine), Geodon® (ziprasidone), clonazepam, and Strattera® (Lilly). The cause of death was ruled a multi-drug overdose due to venlafaxine and atomoxetine, and the manner suicide.

Case 3

A 24-year-old Hispanic male (77 in; 180 lb) with a history of ADHD was found dead on the floor of his home by his caseworker. Autopsy findings showed vomitus around the mouth, left ventricular myocardial hypertrophy with cardiomegaly, and pulmonary congestion and edema. He was prescribed Strattera® 20 mg twice a day. The cause of death was attributed to cardiac arrhythmia due to hypertrophic cardiomyopathy, and the manner of death was ruled natural.

Analytical Method

Extraction

A modified version of a standard organic base extraction procedure (5) revealed the presence of atomoxetine in the aortic (central) blood of the 3 cases presented. Screening analyses were performed on aliquots of blood (2 mL) that had been preserved with at least 2% sodium fluoride and kept refrigerated between 0°C and 6°C from the time of receipt in the laboratory. Postmortem intervals ranged from approximately 24–72 h. Alphaprodine (1 mg/L) was the internal standard. The extracts were transferred to autosampler vials for analysis by gas chromatogra-

phy (GC), equipped with a nitrogen–phosphorous detector (NPD), followed by definitive identification by full scan mass spectrometry (MS).

Quantification of the original blood specimen and analysis of additional specimens collected in each case on the appropriate amount of specimen to fall within the linear range of the assay followed the same extraction procedure with the addition of a standard curve and analyte-specific quality control, utilizing GC/NPD. Liver homogenates (1:4 dilution) were prepared by adding 5 g of the tissue to 15 g of water. The mixture of liver and water was then homogenized with a Polytron® homogenizer (Brinkmann Instruments, Inc., Westbury, NY).

Standard and Control Preparation

Working methanolic spiking solutions of both standards (10, 100 µg/mL) and controls (10 µg/mL) were prepared by serial dilution from a 1 mg/mL stock solution prepared from the powder supplied by the pharmaceutical company. All stock and working solutions were stored between 0°C and 6°C. Calibration curves and quality control samples were created by spiking aliquots of drug-free blood with the working spiking solutions at appropriate concentrations. Confirmation analyses utilized a 5-point calibration curve at concentration levels of 0.2, 0.5, 1.0, 2.0, and 4.0 mg/L, with a positive control sample at 0.5 mg/L. An aliquot of the drug-free blood was analyzed concurrently with each batch as a negative control.

The assay was linear from 0.2 to 10 mg/L with a least-squares linear regression analysis correlation coefficient (r^2) of 0.998 or better. The limits of quantitation and detection were 0.1 and 0.05 mg/L, respectively. Accuracy and precision studies conducted with a control spiked at 0.5 mg/L ($3 \times n = 5$) gave a mean within 8% of the target value (CV = 7%).

GC Analysis

GC/NPD was performed utilizing a Hewlett Packard 6890 GC equipped with a J&W Scientific (Agilent Technologies, Wilmington, DE) DB-5 megabore capillary column (15 m × 0.53 mm i.d. × 1.5 µm film thickness) and an NPD bead (Agilent Technologies). Injections of 1 µL in the splitless mode were made with an inlet temperature of 275°C. Helium was the carrier gas at a flow rate of 6.7 mL/min with an initial oven temperature of 120°C. This was followed by an increase of 15°C/min until 300°C, holding for 3 min.

Drug confirmation by GC/MS was performed on an Hewlett Packard 6890 GC equipped with a J&W Scientific (Agilent Technologies) DB-5MS narrow bore capillary column (15 m × 0.25 mm i.d. × 0.25 µm film thickness) interfaced with a Hewlett Packard 5973 mass selective detector. Split injections (3:1) of 1 µL were made with an inlet temperature of 275°C. Helium was the carrier gas at a flow rate of 1.4 mL/min with an initial oven temperature of 70°C for 2 min. The oven temperature was then ramped up at a rate of 15°C/min until 300°C was reached where it was held for 7 min. Electron impact ionization was utilized in the scan mode, monitoring ions from 40–550 *m/z* ratio. The relative retention time of atomoxetine to alphaprodine was 1.1. Prominent ions (*m/z*) for atomoxetine were 44, 148, and 255.

Results and Discussion

The results of the toxicological analyses for atomoxetine are shown in Table 2. Cases 1 and 3 demonstrate the distribution of atomoxetine in postmortem fluids and tissue in deaths unrelated to atomoxetine. These data compare to data reported by the LA Coroner's Office (chest blood; 0.08–1.3 mg/L: femoral blood; 0.04–0.23 mg/L: vitreous; 0.34 mg/L: bile; 1.5 mg/L: urine; 0.62 mg/L: liver; 4.2 mg/kg: gastric; 1.2 mg/kg) (4) that are considered incidental findings to the cause of death, and the whole blood concentrations fall within the expected therapeutic ranges (Table 1) (3). Full toxicology also revealed the presence of amphetamine (0.37 mg/L) in the aortic blood of Case 1, consistent with her medical history of being prescribed Adderall®, and a trace amount of caffeine. While Case 1 is that of an adolescent, these postmortem concentrations can be compared to other data because atomoxetine pharmacokinetics in pediatric patients and adult subjects are similar after adjustment for body weight (1,2). A trace amount of nicotine was detected in Case 3. No other drugs or ethanol were detected in either case.

Case 2 exemplifies postmortem fluid and tissue distribution in an intentional overdose. The concentrations of atomoxetine are clearly elevated. Also present in aortic blood at elevated concentrations were venlafaxine (100 mg/L), *N*- and *O*-desmethylvenlafaxine (9.9 and 10 mg/L, respectively), and ziprasidone (0.14 mg/L).

There is as yet little information in the literature regarding therapeutic and toxic blood concentrations of atomoxetine, in particular postmortem data. The concentrations of atomoxetine presented in Cases 1 and 3 are consistent with those reported by Anderson et al. (4). Of interest, both decedents described in Cases 1 and 3 had intrinsic morphologic abnormalities of the cardiac muscle, namely arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy, respectively. These structural abnormalities have not been shown to be caused by environmental factors nor induced by drugs. In fact, multiple gene mutations have been implicated in both hypertropic cardiomyopathy (6) and arrhythmogenic right ventricular dysplasia (7). Even so, it could be argued that the use of drugs causing tachycardia might render such individuals, who are already subject to arrhythmias and/or sudden death, at greater risk for these events. Both the amphet-

TABLE 2—*Postmortem fluid and tissue distribution of atomoxetine.*

	Atomoxetine (mg/L or mg/kg*)						
	Aorta Blood	Femoral Blood	Vitreous	Bile	Urine	Liver*	Gastric (mg Total)‡
Case 1	0.65	0.33	0.1	1.0	NA	3.9	0.0097
Case 2	8.3	5.4	0.96	33	NA	29	16.8
Case 3	<0.1	<0.1†	NA	NA	<0.1	<0.44	NA

†Vena cava blood.
‡Total received by laboratory.
NA, not available.

amine and atomoxetine prescribed for ADHD in Cases 1 and 3 may have exacerbated an underlying natural heart disease despite the concentrations of both drugs being within therapeutic range. Case 2 shows levels from an obvious suicide, supported by the extremely high venlafaxine concentrations. It is doubtful if the two drugs lead to each other's toxicity since each were present at concentrations far exceeding therapeutic ranges and would likely have been lethal by themselves. Although both atomoxetine and venlafaxine utilize CYP2D6 in their metabolism, neither one is a potent inhibitor of the iosoenzyme and, therefore, probably did not cause any significant drug–drug interactions.

The low V_d is reflected in the relatively low liver concentrations found in the therapeutic cases and indeed even the overdose case. Despite atomoxetine having a low volume of distribution, it appears it may undergo postmortem redistribution. Utilizing the reported values in the literature (4) in addition to those in the presented cases, atomoxetine displays central-to-peripheral ratios of 0.08/0.04, 1.3/0.23, 0.65/0.33, and 8.3/5.4 (range: 1.5–5.6). The overdose case, which had a significant concentration of atomoxetine in the gastric contents, only showed a central-to-peripheral ratio of 1.5, apparently ruling out diffusion from the stomach. There is always the possibility, however, that the peripheral samples were contaminated by central cavity blood, a problem that is inevitable in nonstandardized blood draws during autopsy. Additionally, variations in the postmortem interval can affect the concentrations observed in blood specimens and must be borne in mind. The vitreous concentrations, not surprisingly, are the lowest since the drug is highly plasma protein bound and would be less able to cross the cell membranes before it becomes extensively metabolized. Concentrations in the bile are higher than blood and because the majority of atomoxetine is eliminated in the urine in the form of polar and conjugated metabolites this suggests enterohepatic recirculation and subsequent renal excretion.

In conclusion, atomoxetine is being detected in medical examiner cases, not surprisingly because it offers a nonstimulant alternative to drug therapy for ADHD, and although it is usually an incidental finding in death investigations, it is useful to know what tissue concentrations to expect in both therapeutic and overdose situations. Atomoxetine can be considered nontoxic at whole blood and liver concentrations below 1.3 mg/L and 5 mg/kg, respectively. Atomoxetine may undergo postmortem redistribution with a central-to-peripheral ratio ranging from 1.5–5.6.

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