J Forensic Sci, July 2004, Vol. 49, No. 4
Paper ID JFS2003056
Available online at: www.astm.org

Luis J. Segura,[1] *M.D. and Begoña Bravo,*[1] *Pharm.*

Postmortem Citalopram Concentrations: Alone or Along with Other Compounds

ABSTRACT: Citalopram, an antidepressant whose use has become more widespread in Spain in recent years participates directly and indirectly in the lethal mechanism in voluntary and involuntary poisonings. There were 30 cases of autopsies in the Madrid region where citalopram and other psychoactive substances (psychotropic drugs, alcohol, opiates) were detected in the corpses. The postmortem citalopram levels in relation to the manner and mechanism of death were evaluated, and a significant difference between the toxic and nontoxic cases ($p < 0.01$) was found. We studied the citalopram blood levels alone and along with other psychoactive products, and these cases were then further divided into those where the compounds were at deadly levels and those which were not. We found a range of citalopram levels between 0.37 and 0.83 μg/mL in which some cases were associated with citalopram toxicity and others were not. Citalopram blood levels of less than 0.35 μg/mL did not lead to fatal poisoning when it was the sole substance detected.

KEYWORDS: forensic science, citalopram, fatal poisoning, blood levels, alcohol

Citalopram, which became available in Spain at the end of the last decade (1) is a second generation antidepressant from the group of those which selectively inhibits serotonin reuptake. The first deaths connected to citalopram were reported in Denmark (2) in 1991, after its introduction for therapeutic use in 1989. In Sweden, it was registered as a medicine in 1992 and two years later, the first deaths caused by overdoses were reported (3).

There are several publications discussing different causes of death where citalopram appears. A study in Denmark (2) covering the years 1989 to 1996 described 92 autopsies where citalopram was present. Between 1992 and 1995, 21 cases were studied in Sweden, eight deaths were attributed directly to citalopram poisoning while in the remaining cases the death was attributed to other drugs and/or alcohol (4). Another study in Sweden of 4196 autopsies during the period 1994–1999 found 44 cases where citalopram was one of the toxic causes of death although the blood level of this psychotropic drug was greater than 0.7 μg/mL in only 22 cases (3).

A project was carried out in Finland between 1990 and 1995 with the aim of discovering the use of antidepressants in suicides. It concluded that toxic tricyclic antidepressants were found in 78% of cases and selective inhibitors of serotonin reuptake (SSRIs) were present in 18%. Moreover one single drug was found in only 14% of cases (5).

Chemically citalopram is 1-[3-(dimetilamino)propil]-1-(4-fluorofenil)-1,3-dihidroisobenzofurano-5-carbonitrilmonohidrobromide. $C_{20}H_{21}FN_2O.BrH$. Preliminary studies of citalopram kinetics on humans carried out by Overø in 1978, demonstrated quick absorption and a slow elimination (6). The drug is absorbed well when consumed orally with bioavailability of over 95%, and a t_{max} of 2 h, C_{max} 245–395 nmol/L (7), Vd of 12–16 l/kg, clearance 0.41–0.43 l/min by hepatic metabolism (85%) and renal excretion (15%). The average half-life was 33 h. Citalopram (8) undergoes hepatic metabolism through the action of the cytochrome P_{450} (CYP3A4 and 2C19) making way for a demethylated metabolite (N-demethyl) which is further broken down to di-desmethyl citalopram, both of which are present at low levels in serum and have little pharmacological activity. Other metabolites include citalopram N-oxide and an inactive metabolite citalopram propionic acid.

The toxic symptoms produced by citalopram with doses reported up to 600 mg include nausea, tachycardia, dizziness, shaking and drowsiness. Above this amount changes in ECG (QRS prolongation, changes in ST), tachycardia, muscular hyperactivity leading to seizures and moderate CNS depression are observed. Generalized seizures are the most common symptoms in these poisonings when the dose is between 15 and 30 times the therapeutic dose (20 mg/24 h) (9).

Citalopram blood levels between 0.03 and 0.63 μg/mL are described as therapeutic with an average of 0.21 μg/mL by Worm et al. (2), a range of between 0.06 and 0.13 μg/mL and an average of 0.08 μg/mL by Kragh–Sørensen (7). Druid et al. (4) consider levels of between 0.06 and 0.42 μg/mL to be therapeutic. In a recent collection of blood levels of drugs and chemical products, concentrations of between 0.081 and 0.16 μg/mL were considered therapeutic (10).

Citalopram blood levels when citalopram alone was the cause of death, varied between 2.1 and 6.5 μg/mL according to Worm et al. (2) in the four cases studied; Druid et al. (4) claim eight cases with lethal levels (in femoral blood) from 3.5 to 11 μg/mL. Winek's results range between 0.24 and 1.30 μg/mL (10). When other psychoactive drugs and/or alcohol are included the following lethal levels of citalopram are obtained: 0.6–5.4 μg/mL (2), 0.7–4.9 μg/mL (4).

The determination of citalopram and its metabolites in biological samples have been carried out by different chromatographic procedures: thin-layer (TLC) with fluorometric quantification (11), high performance liquid chromatography (HPLC) (8,12,13) and gas chromatography with mass spectrometry (14).

The object of this study is to evaluate the citalopram blood levels detected in biofluids in relation to the manner and mechanisms of death in the cases analyzed in the Madrid Toxicology Laboratory IAF, comparing the citalopram blood levels in cases where the drug was present on its own and with those cases where it was present

[1] Toxicology Laboratory, Instituto Anatómico Forense of Madrid (IAF).

Received 14 Feb. 2003; and in revised form 17 June 2003, 13 Oct. 2003, and 3 Feb. 2004; accepted 4 Feb. 2004; published 13 May 2004.

with other psychoactive substances (alcohol, drugs of abuse, psychotropic drugs) and comparing our results with those reported by other authors.

Materials and Methods

In the present study, we included medico legal cases where citalopram was detected in biological samples obtained at autopsies that took place in the Madrid Instituto Anatómico Forense (IAF), coming from the Madrid region during 2000, 2001 and the first six months of 2002. Previous to 2000 the presence of this antidepressant was not found.

The test group studied is comprised of 30 postmortem cases subjected to legal investigation where the presence of citalopram was detected in the biological samples analyzed. The 30 deaths were comprised of 19 males and 11 females between the ages of 26 and 85 (mean 50).

The biological samples analyzed were: blood (30 samples), urine (10 samples) and gastric content (7 samples). The samples were taken, bottled and labeled according to the rules set up for legal autopsies (15) which include chain of custody. Immediately after collection, the samples were kept at a temperature of −20°C in the laboratory and they were all analyzed within 48 h.

Experimental

Reagents

Citalopram.HBr supplied by Lundbeck (Copenhagen, Denmark), proadifen.HCl from Sigma-Aldrich Inc. (St. Louis, MO), potassium-dihydrogen phosphate, N-propanol, methanol, acetone, acetic acid, trichloromethane, ethyl acetate, ammonium, all with analytical quality or HPLC grade obtained from Merck (Darmstadt, Germany). N-Methyl-bis-(trifluoroacetamide) (MBTFA) and 2,2,2-Trifluoro-N-Methyl-N-(Trimethylsilyl)-acetamide (MSTFA) from Sigma-Aldrich Inc. (St. Louis, MO). Water deionized by Milli-Q station (Millipore, Bedford, MA) was used in all the experiments.

Instrumentation

The following instruments were used: Bransonic® Ultrasonic Cleaner 1200E-1 from Branson Ultrasonics Corporation (CO), Sep-Pak Vacuum Station 20 from Waters (MA), TurboVap® LV Evaporator from Zymark (MA), chromatography of liquids Remedi HS™ Drug Profiling System from Bio-Rad (CA), chromatography of gases Auto System XL with FID detector and injector Headspace Sampler-40 from Perkin Elmer (CT), gas chromatography Hewlett-Packard HP 6890 series GC system equipped with automatic injector, 100 route sampler and quadruple mass spectrometer HP 5972 MS (Geneva, Switzerland).

Analytical Processing

Standard Reference Solution

A stock solution of 1 mg/mL of citalopram was prepared in methanol, from which a 100 μg/mL working solution was prepared. The internal standard working solution from proadifen was also 100 μg/mL. The stock solutions were stored at −20°C.

Calibration Solution

Solutions from blank samples of blood and urine were prepared and citalopram stock solution was added in order to obtain a range of levels between 0.1 and 15 μg/mL (0.1, 0.5, 1, 5, 10, 15 μg/mL). Linear calibration curves with coefficient of correlation (r^2) ≥ 0.993 were obtained.

Quality of Analytical Procedure

The limit of detection was the mean value from the blank sample result plus 3 times the standard deviation, and the quantification limit from the blank sample result plus 10 times the standard deviation; all the results are above these limits. The accuracy and precision of the analysis were carried out by means of analysis of 10 samples at 2 levels of concentration. We calculated regression analysis (Cochran's test), variance analysis (Fisher's distribution) and confidence intervals for linearity of the assay.

Preparation and Extraction

Six milliliters are taken from each one of the blood and urine samples for screening by the Remedi HS system and 3 mL for confirmation and quantification by Hewlett Packard HP 6890 series GC-MS to which 10 μL of the working solution internal standard (proadifen) was added. After conditioning, the pH of the samples with buffer phosphate pH 6 they are sonicated for 30 min and then centrifuged at 3500 rpm/10 min, the supernatant was used for SPE procedure in Sep Pak Vacuum Station 20. The extraction columns used were Waters, Oasis MCX which are conditioned beforehand with 2 mL of methanol followed by 2 mL of buffer phosphate pH 6. After adding the sample and cleansing with 2 mL of deionized water, 0.5 mL of acetic buffer pH 4 is added. After drying the column a first elution is carried out with 4 mL of acetone:trichloromethane (1:1 v/v) and a second with ethyl acetate with 2% ammonia. The two mixed eluates are dried under nitrogen flow at 40°C in a Turbovap LV Evaporator and reconstituted with 2 mL of buffer phosphate pH 6 for analysis on the Remedi HS system. For the analysis by GC-MS, 20 μL of MBTFA is added to the final eluate and then dried in a nitrogen current at 40°C in Turbovap LV Evaporator, afterwards 100 μL of MSTFA is added and incubated for 5 min at 60°C. After leaving to cool, 20 μL of MBTFA is added incubating at the same temperature for 10 min. Derivatization with MBTFA was used to estimate the amounts of other drugs and is not required for analysis of citalopram.

Chromatographic Conditions

Remedi HS is a system of high performance liquid chromatography HPLC with a multi column design and ultraviolet detector (193–305 nm), which is accompanied by an extensive library with 920 drugs and metabolites (Drug library $4.3 \times .21/5. \times \times .21$) whose usefulness in the fields of forensic and clinical science have been studied by different authors (16–18). The analysis period lasts approximately 16 min. The system uses a mixture of internal standards (nordiazepam-N-ethyl and chlorpheniramine) which must be added to the samples. Citalopram presents a maximum λ of 244 the same as its metabolites. The relative time with regard to the internal standard nordiazepam-N-ethyl is 2.796 and relating to chlorpheniramine is 0.569. The relative time relating to its metabolites is shorter.

Hewlett Packard HP6890 Series GC MS

The chromatographic conditions of the oven were as follows: starting temperature of 60°C for 2 min which is increased at a rate of 10°C/min until it reaches 295°C where it remains for 1 min. The column used was a HP-5MS (15 m × 0.25 mm × 0.25 μm)

with a Helium flow of 1 mL/min. The injections took place using splitless (2 μL) to a temperature of 250°C. We worked with an EM of 400 + Autotune with a solvent delay of 3.50. The interface temperature was 280°C. The analysis was done in both scan mode and SIM, the ions monitored were for citalopram m/z (324), 238, 208 and 58; citalopram N-desmethyl m/z (238), 310, 208 and 138; the didemethyled metabolite m/z (238), 320, 261, 208, and for internal standard proadifen m/z (86), 99, 165 and 238.

Results

During 2000 and 2001 and the first six months of 2002, 5397 legal autopsies were carried out in Madrid (IAF), and a toxicology study was applied to 1684 of these cases. We detected citalopram in 30 cases (0.55%). The first case in which this antidepressant was detected was discovered in January 2000 and the cause of death was voluntary suffocation. All the cases in which citalopram was identified are included. There were no cases of homicide.

Table 1 shows the characteristics of the 30 cases studied including gender, age, citalopram level in cardiac blood (right atrium), in urine, in gastric content and alcohol level in blood. Other substances detected in the analysis of the blood sample and the official manner and mechanism of death are also included.

The subjects had a mean age of 50 (ranging from 26 to 85; median 47; SD 15.26). Nineteen (63%) are male and 11 are female (37%). The manner of death was suicide in 20 cases (67%), accidental death in 8 (27%) and 2 deaths were from natural causes. The most frequent fatal mechanism was intoxication by drugs which includes the presence of citalopram, on its own or along with other psychoactive drugs. That mechanism was found in 14 cases (47%) of which 9 were suicides and 5 accidental deaths. The next most frequent mechanism of death is jumping from a height (6 cases).

Citalopram Levels According to the Manner of Death—In suicide cases (20 cases) the mean blood level is 1.83 μg/mL (ranging from 0.04–13.9), in accidental deaths (8 cases) the average blood level taken is 1.12 μg/mL (ranging from 0.09–5.72). There are no significant differences with regard to the manner of death.

Citalopram Levels According to Fatal Mechanism—The average citalopram blood level in cases of intoxication (14 cases) was 2.58 μg/mL (SD 3.92) (Table 2), whereas when the mechanism was precipitation, hanging or other types of nonintoxication (16 cases) the median level was 0.60 μg/mL (SD 0.74) (Table 3). A significant difference was noted ($p < 0.05$) when the comparison of the average levels was carried out.

Citalopram Levels According to Manner and Fatal Mechanisms—In suicide cases: in those provoked by intoxication (9 cases) the average citalopram level is 3.26 μg/mL (ranging from 0.3–13.9) and in the case of nontoxic (5 cases) the average blood level found was 0.65 μg/mL (ranging from 0.04–3.1). Comparing the averages we get a result of $p < 0.1$.

For accidental deaths, we saw that in the case of intoxication with psychoactive substances (5 cases), the average is 1.37 μg/mL (ranging from 0.09–5.72) while in the remaining cases (3 cases), it was 0.72 μg/mL (ranging from 0.4–1.37).

Citalopram Levels Depending on the Presence of Alcohol— The alcohol tests were carried out in all cases. There were 10 positive cases: 7 suicides and 3 accidental deaths. The highest concentrations (above 0.35 g/dL) were found in 3 of the suicides (0.38, 0.41, 0.42 g/dL). In one of the suicides by intoxication, the alcohol detected was methanol which has a concentration of 0.5 g/dL.

The average citalopram level in the blood in these cases (20 cases) where the presence of alcohol was not detected was 0.99 μg/mL (median 0.4; SD 1.63). However, when alcohol was identified (10 cases), the average citalopram level was 2.61 μg/mL (median 0.7; SD 4.08).

Blood Citalopram Levels Related to the Presence of Other Drugs—In cases where citalopram was the only substance detected (5 cases) levels ranged between 0.04–6.83 μg/mL (median 0.35), the one with the highest concentration being a case of suicide by poisoning. Furthermore, there is a case which contains the local anaesthetic mepivacaine where the blood citalopram concentration is 0.40 μg/mL.

Citalopram mixed solely with ethanol is present in 3 cases (2 suicides and 1 accidental death), the levels of the antidepressant range between 0.30 and 13.9 μg/mL and the levels of alcohol were 0.06, 0.26, and 0.42 g/dL.

The mixture of benzodiacepines and citalopram, where no other psychoactive substance was detected, appears in 7 cases with a range of citalopram of between 0.09 and 0.41 μg/mL (average 0.94; median 0.47).

When the mixture of psychoactive substances detected includes citalopram, benzodiazepines and ethanol, 2 cases can be appreciated, one of which contains carbon monoxide with a concentration of 45% in the blood.

The series of cases which include the presence of citalopram, benzodiazepines and other psychoactive substances is composed of 7 cases with citalopram levels of between 0.09 and 5.72 μg/mL (average 1.45; median 0.68). In 3 of them, alcohol was not detected and of the remaining (4 cases) one contained methanol (0.5 g/dL) and ethanol in the others (0.02, 0.25, and 0.41 g/dL). In 4 cases, opiates were detected (morphine, codeine and dextrometorphan), furthermore in one of them, there were traces of cocaine. Other psychotropic drugs detected in this group are: maprotiline, olanzapine and levomepromazine.

In the 5 remaining cases, there is another substance (tramadol, mirtazapine, venlafaxine, clozapine and others) along with citalopram, the concentrations range from 0.01 to 0.77 μg/mL.

Discussion

The series of cases that we present shows that the victims ages were similar to those published by other authors (2,9,19); however, there is no predominance of females because practically two thirds of our sample is male.

We found three kinds of manner of death: the most common is suicide followed by accidental death and only two deaths by natural causes (acute myocardial heart attack and cardiogenic shock). The greater proportion of suicide cases gives rise to a false figure in the study group due to the typical characteristics of those victims who usually mix different psychotropic medication within their medical treatment (antidepressant, antipsychotics, benzodiazepines). On some occasions, they use poisonous doses along with other fatal methods to ensure that death occurs. Lethal blood levels published by Winek et al. in "Drug and chemical blood level data 2001" (0.24–1.3 μg/mL) may have included cases with other drugs or alcohol. The poisonous suicides show high blood citalopram levels and all are above the lethal range.

In non-suicidal poisonings, morphine and codeine appear along with citalopram; in three cases, the morphine level is lethal and in one case cocaine is detected. We draw the conclusion that it is a case of a drug addict on psychotropic drug treatments whose deadly poisoning mechanism is a combination of drug abuse and citalopram.

In the cases where the fatal mechanism isn't toxic (Table 3), we can see citalopram blood levels which are considered lethal by some authors (10,19) in 12 cases and non-lethal in four cases. There are

TABLE 1—*The 30 cases with citalopram: gender, age, citalopram concentrations (blood, urine and gastric content), blood alcohol concentration, other compounds found in the toxicological blood analyses, manner of death and mechanism of death.*

No.	Gender & Age (years)	Citalopram Blood (μg/mL)	Citalopram Urine (μg/mL)	Citalopram Gastr.-Cont (μg/mL)	Ethanol Blood (g/dL)	Other Drugs (μg/mL)	Manner of Death	Mechanism of Death
1	m 64	0.28		0.33	0.00	Maprotiline 0.13 Nordiazepam 0.12	Suicide	Suffocation
2	f 81	0.01		nd	0.00	Tramadol 0.10	Natural	C. Shock
3	f 46	0.30			0.42		Suicide	Intoxication
4	f 52	0.09			0.00	Nordiazepam 0.04	Suicide	Jumping
5	m 40	0.09			0.00	Codeine 0.04 Morphine 0.20 Nordiazepam 4.56	Accidental	Intoxication
6	f 75	0.75			0.00	Mirtazapine	Suicide	Jumping
7	m 42	1.37			0.10	Diazepam 0.06 COHb 45%	Accidental	Burning
8	f 39	5.72	2.79		0.35	Cocaine 0.11 Codeine 0.01 Morphine 0.19 Nordiazepam 3.24	Accidental	Intoxication
9	m 36	0.77			0.00	Venlafaxine 2.20	Suicide	Slitting of the throat
10	m 58	0.83	6.41		0.00	Diazepam 0.76 Oxazepam 0.17	Suicide	Jumping
11	m 26	3.10			0.00		Suicide	Traffic (train)
12	m 35	0.74	5.50		0.00	Nordiazepam 0.04	Accidental	Intoxication
13	m 48	2.51	19.77	65.51	0.02	Alprazolam 1.24 Olanzapine 0.01	Suicide	Intoxication
14	m 35	13.9			0.06		Suicide	Intoxication
15	m 56	0.72			0.41	Methotrimeprazine 0.05 Nordiazepam 0.78	Suicide	Intoxication
16	m 68	0.35			0.00		Natural	Myocardial heart attack
17	f 36	0.68			0.50*	Diazepam 0.08 Dextromethorphan 0.04 Nordiazepam 0.20	Suicide	Intoxication
18	m 38	0.10	5.81		0.00	Buflomedil 0.60 Codeine 0.04 Morphine 0.01 Thioridazine-2-S 0.04	Accidental	Intoxication
19	f 50	0.19	0.6	0.19	0.38	Nordiazepam 0.15	Suicide	Jumping
20	m 62	0.47	nd	5.19	0.00	Aminophenazone 0.51 Flurazepam 0.03 Flurazepam met. 0.11	Suicide	Intoxication
21	m 60	0.42			0.00	Nordiazepam 0.04	Suicide	Hanging
22	m 33	0.40			0.26		Accidental	Jumping
23	m 33	0.20	5.79		0.00	Codeine 0.04 Morphine 0.14 Nordiazepam 0.83	Accidental	Intoxication
24	f 42	0.37	1.72	10.02	0.20	Clozapine 1.09	Suicide	Intoxication
25	f 41	0.34	6.43		0.00		Suicide	Jumping
26	m 40	0.04			0.00		Suicide	Hanging
27	f 57	3.62		47.20	0.00	Diazepam 1.63 Nordiazepam 3.85	Suicide	Intoxication
28	f 85	6.83			0.00		Suicide	Intoxication
29	m 63	0.40			0.00	Mepivacaine 4.20	Accidental	Road Traffic
30	m 63	0.41			0.00	Diazepam 0.17 Nordiazepam 0.51	Suicide	Traffic (train)

* Methanol.

nd: not detected.

two cases with special circumstances which could have artificially raised the citalopram blood levels: no. 7 shows a reading of 45% of carboxyhemoglobin (after death in a road accident followed by the burning of the car) and no. 11 who was killed by being run over by a train. In both cases, there was probable contamination of the blood samples analyzed with tissues and other biofluids. Moreover in case 7, the extremely high temperature that the corpse was subjected to could have altered the conditions of the sample. These two cases are ignored for the purpose of the discussion.

Our results indicate citalopram levels—as the sole substance detected in blood—of less than 0.35 μg/mL, didn't lead to deadly poisoning (Table 4).

In the case of nontoxic deaths when citalopram was taken along with psychoactive substances that didn't show lethal levels (Group E, Table 4), a range of 0.01 to 0.83 μg/mL (average 0.43 μg/mL) were found; however, in deaths with deadly poisoning mechanism, the same type of association (Group B, Table 4) offers a range of 0.37 to 13.9 μg/mL (average 3.82) which indicates the

TABLE 2—*The 14 cases whose mechanism of death was* Intoxication: *blood concentrations of citalopram, benzodiazepines, antipsychotics, opiates, and other compounds found in toxicological analyses.*

No.	CIT (μg/mL)	Alcohol (g/dL)	Benzodiazepines (μg/mL)	Antipsychotics (μg/mL)	Opiates (μg/mL)	Others (μg/mL)
3	0.30	0.42				
5	0.09	0.00	Nordiazepam 4.56		Codeine 0.04 Morphine 0.20	
8	5.72	0.35	Nordiazepam 3.24		Codeine 0.01 Morphine 0.19	Cocaine 0.11
12	0.74	0.00	Nordiazepam 0.04			
13	2.51	0.02	Alprazolam 1.24	Olanzapine 0.01		
14	13.9	0.06				
15	0.72	0.41	Nordiazepam 0.78	Methotrimeprazine 0.05		
17	0.68	0.50*	Diazepam 0.08 Nordiazepam 0.20		Dextromethorphan 0.04	
18	0.10	0.00		Thioridazine-2-S 0.04	Codeine 0.04 Morphine 0.01	Buflomedil 0.60
20	0.47	0.00	Flurazepam 0.03 Flurazepam Met. 0.11			Aminophenazone 0.51
23	0.20	0.00	Nordiazepam 0.83		Codeine 0.04 Morphine 0.14	
24	0.37	0.20		Clozapine 1.09		
27	3.62	0.00	Diazepam 1.63 Nordiazepam 3.85			
28	6.83	0.00				

* Methanol
CIT: citalopram.

TABLE 3—*The 16 cases whose mechanism of death was* Not Intoxication: *blood concentrations of citalopram, benzodiazepines, antidepressants, opiates, and other compounds found in toxicological analyses.*

No.	CIT (μg/mL)	Alcohol (g/dL)	Benzodiazepines (μg/mL)	Antidepressants (μg/mL)	Opiates (μg/mL)	Others
1	0.28	0.00	Nordiazepam 0.12	Maprotiline 0.13		
2	0.01	0.00			Tramadol 0.10	
4	0.09	0.00	Nordiazepam 0.04			
6	0.75	0.00		Mirtazapine		
7	1.37	0.10	Diazepam 0.06			COHb 45%
9	0.77	0.00		Venlafaxine 2.20		
10	0.83	0.00	Diazepam 0.76 Oxazepam 0.17			
11	3.10	0.00				
16	0.35	0.00				
19	0.19	0.38	Nordiazepam 0.15			
21	0.42	0.00	Nordiazepam 0.04			
22	0.40	0.26				
25	0.34	0.00				
26	0.04	0.00				
29	0.40	0.00				Mepivacaine 4.2 μg/mL
30	0.41	0.00	Diazepam 0.17 Nordiazepam 0.51			

CIT: citalopram.

existence of a group of results whose concentrations are shared by both groups. Due to this, a reasonable doubt is produced regarding the possible death mechanism where citalopram concentrations are between 0.37 and 0.83 μg/mL.

If we analyze the combination of citalopram and psychoactive substances with lethal levels (Group C, Table 4), we don't note a significant difference in the range of the antidepressant being studied with respect to the groups previously evaluated (Group B and Group E, Table 4). The concentration of the other substances therefore doesn't seem to influence the citalopram levels.

In comparison with the details presented by Worm et al. (2) where deaths are produced by citalopram mixed with other compounds, our range of results has a smaller lower limit. Regarding the levels published by Winek (10) that we took as reference, we believe that the fatal range of citalopram, where its the sole toxic substance present, must have its lower limit raised to 0.35 μg/mL.

On comparing the average citalopram levels between the group where the mechanism of death was poisoning and those with different (nontoxic) mechanisms, there is a substantial statistical difference with $p < 0.01$. The levels are much higher in the intoxication group.

The consumption of alcohol along with citalopram is produced in a third of the cases studied, the blood alcohol concentration (BAC) in the whole cross section was 0.07 g/dL with important differences being found between the toxic deaths (average 0.10 g/dL) and the nontoxic cases (0.04 g/dL). Our results are comparable to those

TABLE 4—*Median, mean and range of citalopram concentrations in accordance with mechanism of death and substance association in autopsy cases.*

Mechanism of Death	Group	Material	Citalopram µg/mL	No. of Cases	Mean µg/mL	Median µg/mL
TOXIC	Group A					
	Citalopram alone	Blood	6.83	1		
	Group B					
	Citalopram +	Blood	0.37–13.9	5	3.82	0.74
	Others (not lethal level)	Urine	0–1.72	3		
		Gastric C.	5.19–47.2	3		
	Group C					
	Citalopram +	Blood	0.09–5.72	7	1.46	0.68
	Others (lethal level)	Urine	2.79–19.77	3		
NONTOXIC	Group D					
	Citalopram alone	Blood	0.04–0.35	3	0.24	0.34
		Urine	6.43	1		
	Group E					
	Citalopram +	Blood	0.01–0.83	10	0.43	0.40
	Others (not lethal level)	Urine	6.41	1		

which Jonasson (19) found and whose average is 0.13 g/dL. In contrast to Worm (2), we didn't find lower citalopram levels mixed with alcohol, quite the opposite, because the average citalopram level when alcohol is present is 2.61 µg/mL whereas when alcohol is not detected the average level is 0.99 µg/mL ($p < 0.1$).

We believe it is necessary to continue researching more cases in order to be able to delimit the lethal toxic levels of citalopram when it is mixed with other drugs and depending on the concentrations (lethal or not) of these drugs in the blood.

Acknowledgments

The authors would like to thank the collaboration of the Toxicology Laboratory staff, the Comunidad de Madrid Forensic Medical Doctors, and the Instituto Anatómico Forense staff.

References

1. Boletín Informativo. Servicio de Farmacia. M°. de Sanidad. November. 1998. Spain.
2. Worm K, Dragsholt C, Simonsen K, Kringsholm B. Citalopram concentrations in samples from autopsies and living persons. Int J Legal Med [PubMed] 1998;111:188–90.
3. Ostrom M, Eriksson A, Torzón J, Spigset O. Fatal overdose with citalo- [PubMed] pram. Lancet 1996;348:339–40.
4. Druid H, Holmgren P. A compilation of fatal and control concentrations of drugs in postmortem femoral drugs. J Forensic Sci 1997;42: [PubMed] 79–87.
5. Ohberg A, Vuori E, Klaukka T, Lonnqvist J. Antidepressants and suicide [PubMed] mortality. J Affect Disord 1998;50:225–33.
6. Overø KF. Preliminary studies of the kinetics of citalopram in man. Eur J Clin Pharmacology 1978;14:69–73.
7. Kragh-Sørensen P, Overø KF, Petersen OL, Jensen K, Parnas W. The kinetics of citalopram: single and multiple dose studies in man. Acta Pharmacol et Toxicol 1981;48:53–60.
8. Kristoffersen L, Bugge A, Lundanes E, Slørdal L. Simultaneous determination of citalopram, fluoxetine, paroxetine and their metabolites in plasma and whole blood by high-performance liquid chromatography with ultraviolet and fluorescence detection. J Chromatogr B 1999;774:229–46.
9. Personne M, Sjöberg G, Persson H. Citalopram overdose-review of cases treated in Swedish hospitals. Clin Toxicol 1997;35:237–40.
10. Winek CL, Wahba WW, Winek Jr. CL, Balzer TW. Drug and chemical blood-level data 2001. Forensic Sci Int 2001;122:107–23. [PubMed]
11. Overø K F. Fluorescence assay of citalopram and its metabolites in plasma by scanning densitometry of thin-layer-chromatograms. J Chromatogr 1981;224:526–31.
12. Øyehaug E, Østensen ET. High-performance liquid chromatographic determination of citalopram and four of its metabolites in plasma and urine samples from psychiatric patients. J Chromatogr 1984;308:199–208. [PubMed]
13. Macek J, Ptáček P, Klíma J. Rapid determination of citalopram in human plasma by high-performance liquid chromatography. J Chromatogr B 2001;755:279–85.
14. Eap CB, Bouchoux G, Amey M, Cochard N, Savary L, Baumann P. Simultaneous determination of human plasma levels of citalopram, paroxetine, sertraline, and their metabolites by gas chromatography-mass spectrometry. J Chromatogr Sci 1998;36:365–71. [PubMed]
15. Orden Ministerial del Ministerio de Justicia. 8 November 1996, BOE 23, December 1996.
16. Kalasinsky KS, Schaefer T, Binder SR. Forensic application of an automated drug-profiling system. J Anal Tox 1995;19(6):412–8.
17. Demedts P, Wauters A, Frandk F, Neels H. Evaluation of the REMEDI drug-profiling system. Eur J Clin Chem Clin Biochem 1994;32(5):409–17. [PubMed]
18. Ohtsuji M, Lai JS, Binder SR, Kondo T, Takayasu T, Ohshima T. Use of REMEDI HS in emergency toxicology for a rapid estimate of drug concentrations in urine, serum, and gastric samples. J Forensic Sci 1996;41(5):881–6. [PubMed]
19. Jonasson B, Saldeen T. Citalopram in fatal poisoning cases. Forensic Sci Int 2002;126:1–6. [PubMed]

Additional information and reprint requests:
Luis J. Segura, M.D.
Laboratorio de Toxicología, Instituto Anatómico Forense
Ciudad Universitaria, Pabellón 7
28040—Madrid, Spain
Fax: 34 915441087
E-mail: lseguraa@meditex.es