Simultaneous Determination of Human Plasma Levels of Citalopram, Paroxetine, Sertraline, and Their Metabolites by Gas Chromatography–Mass Spectrometry

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Abstract

A gas chromatography–mass spectrometry method is presented which allows the simultaneous determination of the plasma concentrations of the selective serotonin reuptake inhibitors citalopram, paroxetine, sertraline, and their pharmacologically active *N*-demethylated metabolites (desmethylcitalopram, didesmethylcitalopram, and desmethylsertraline) after derivatization with the reagent *N*-methyl-bis(trifluoroacetamide). No interferences from endogenous compounds are observed following the extraction of plasma samples from six different human subjects. The standard curves are linear over a working range of 10–500 ng/mL for citalopram, 10–300 ng/mL for desmethylcitalopram, 5–60 ng/mL for didesmethyl-citalopram, 20–400 ng/mL for sertraline and desmethylsertraline, and 10–200 ng/mL for paroxetine. Recoveries measured at three concentrations range from 81 to 118% for the tertiary amines (citalopram and the internal standard methylmaprotiline), 73 to 95% for the secondary amines (desmethylcitalopram, paroxetine and sertraline), and 39 to 66% for the primary amines (didesmethylcitalopram and desmethylsertraline). Intra- and interday coefficients of variation determined at three concentrations range from 3 to 11% for citalopram and its metabolites, 4 to 15% for paroxetine, and 5 to 13% for sertraline and desmethylsertraline. The limits of quantitation of the method are 2 ng/mL for citalopram and paroxetine, 1 ng/mL for sertraline, and 0.5 ng/mL for desmethyl-citalopram, didesmethylcitalopram, and desmethyl-sertraline. No interferences are noted from 20 other psychotropic drugs. This sensitive and specific method can be used for single-dose pharmacokinetics. It is also useful for therapeutic drug monitoring of these three drugs and could possibly be adapted for the quantitation of the two other selective serotonin reuptake inhibitors on the market, namely fluoxetine and fluvoxamine.

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Introduction

Citalopram (CIT), paroxetine (PAR), and sertraline (SER) (Figure 1) are new antidepressants belonging to the class of the selective serotonin reuptake inhibitors (SSRIs). They exhibit clin-

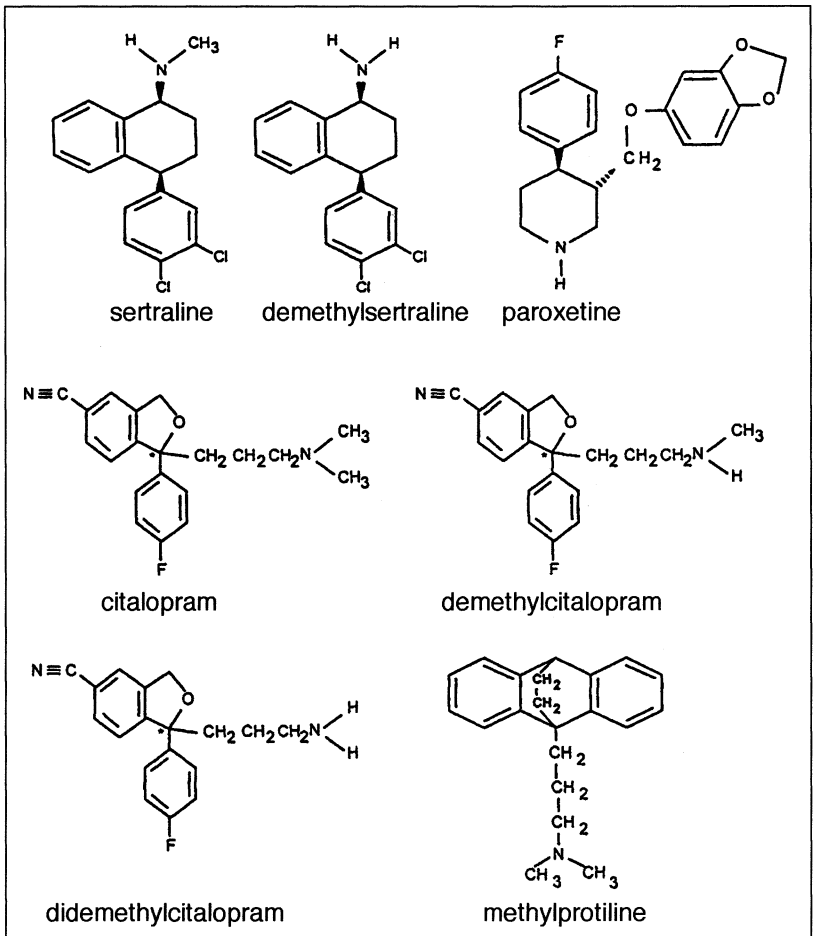

Figure 1. Chemical structures of CIT, DCIT, DDCIT, PAR, SER, DSER, and MMP (internal standard).

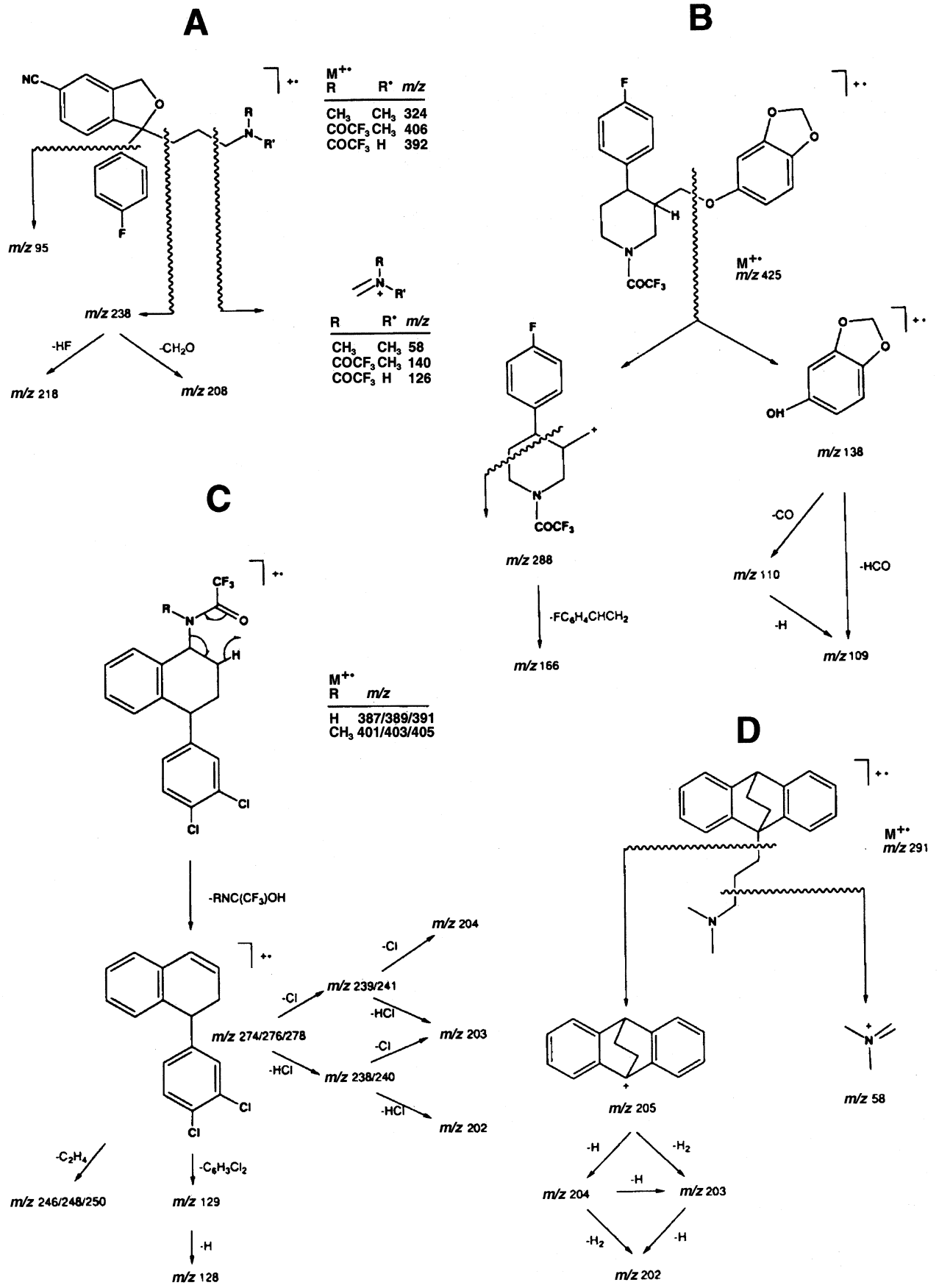

Figure 2. The most probable fragmentation pathways of the molecular cations of CIT (A), PAR (B), SER (C), and MMP (D).

ical efficacy comparable to that of classical tricyclic antidepressants, but they are devoid of some of the adverse anticholinergic and cardiovascular effects commonly associated with these drugs (1). In the organism, these SSRIs are biotransformed to *N*-demethylated metabolites (2). Desmethylparoxetine is considered pharmacologically inactive, whereas desmethylcitalopram (DCIT), and perhaps also desmethylsertraline (DSER), contribute to the pharmacological activity of their parent drug (2).

Although no therapeutic windows have been defined for SSRIs in contrast to tricyclic antidepressants, analytical methods for therapeutic drug monitoring of SSRIs are useful in several instances. They are necessary for pharmacokinetic experiments, but one of their major potential uses is to check compliance. It has been shown that up to one-third of patients stop taking their antidepressants after six weeks, two-thirds of whom do not report it to their general practitioner (3). Several thin-layer chromatography, high-performance liquid chromatography (HPLC), or gas chromatography (GC) methods have been published (4) for the determination of the five SSRIs presently on the market (CIT, PAR, SER, fluoxetine [FLX], fluvoxamine [FLV]) and their metabolites in plasma or serum samples. Recently, we described a GC–mass spectrometric (GC–MS) method which allows the simultaneous determination of the enantiomers of FLV and either FLX or norfluoxetine (NFLX) after derivatization with (*S*)-(–)*N*-trifluoroacetylprolyl chloride (5). To our knowledge, this is the only published method which allows the simultaneous determination of two SSRIs (5). Such methods would not only decrease the cost and speed up analysis, but would also be useful when two SSRIs are administered simultaneously (4). In the present paper, we describe a sensitive and specific GC–MS method which simultaneously measures CIT, SER, PAR, and their *N*-demethylated pharmacologically active metabolites.

Experimental

Reagents

CIT hydrobromide, DCIT hydrochloride, and didesmethylcitalopram (DDCIT) *L*-tartrate monohydrate were supplied by Lundbeck (Copenhagen, Denmark). SER hydrochloride and

Table I. Main Ions (*m/z*) and Relative Abundance (%) in the Mass Spectra of CIT, PAR, SER, Their *N*-Demethylated Metabolites, and MMP after Derivatization with *N*-Methyl-bis(trifluoroacetamide)

CIT		DCIT		DDCIT		PAR		SER		DSER		MMP	
m/z	Relative abundance (%)	*m/z*	Relative abundance (%)	*m/z*	Relative abundance (%)	*m/z*	Relative abundance (%)	*m/z*	Relative abundance (%)	*m/z*	Relative abundance (%)	*m/z*	Relative abundance (%)
58	1000*	238	1000*	238	1000*	138	1000*	274	1000*	274	1000*	58	1000*
324	31†	58	8	69	47	425	467†	402	723†	388	52†	291	98†
56	12	60	8	75	15	69	67	69	140	101	198	42	39
59	39	69	44	78	14	79	41	101	273	115	149	43	17
70	7	75	10	95	34	107	53	102	126	116	80	44	13
71	21	78	9	109	23	109	483	110	227	127	74	45	41
73	10	95	23	114	13	110	83	115	198	128	232	56	13
75	6	109	18	115	19	115	50	127	227	129	161	59	38
84	11	110	9	116	14	121	68	128	335	146	90	70	11
86	4	114	8	123	19	122	43	129	352	159	206	71	20
95	12	115	12	126	28	123	62	159	599	161	138	73	45
109	9	116	10	127	9	126	38	160	293	172	144	84	29
114	4	123	15	140	10	133	111	161	416	174	90	85	20
115	7	140	52	154	9	135	521	202	330	202	172	165	19
123	7	168	10	181	10	137	45	203	301	203	180	176	22
181	4	181	8	183	50	139	107	204	185	204	174	177	11
182	5	183	41	184	13	140	110	238	246	215	150	178	31
183	12	184	12	190	59	146	57	239	225	238	95	189	53
190	14	190	51	191	10	147	161	240	208	239	219	190	22
208	27	191	9	195	12	148	37	242	128	240	87	191	55
209	9	195	10	208	83	149	43	275	313	241	81	192	10
218	8	208	71	209	23	151	56	276	676	246	120	201	10
220	10	209	20	218	61	161	90	277	177	248	100	202	66
221	9	218	52	220	63	166	298	278	127	259	85	203	72
238	36	220	54	221	44	175	200	302	133	275	240	204	58
239	6	221	39	222	10	192	49	386	144	276	650	205	25
325	7	222	9	234	11	234	59	400	869	277	137	215	18
		234	9	239	170	288	183	401	947	278	113	217	13
		239	171	240	18	426	109	403	606	387	174	218	14
		240	18	374	14			404	198	389	113	292	23
		388	17										

* Base peak.
† M+.

N-DSER maleate were obtained from Pfizer (Groton, CT). PAR hydrochloride was provided by SmithKline Beecham (Worthing, United Kingdom). *N*-MMP was supplied by Novartis (Basel, Switzerland). *N*-Methyl-bis(trifluoroacetamide) was from Fluka (Buchs, Switzerland). Stock solutions of CIT, DCIT, and DDCIT were prepared using 10 ng/µL of each drug in 0.1M HCl, and stock solutions of PAR, SER, and DSER were prepared using 100 ng/µL of each drug in 0.1M HCl. Working solutions were prepared using 10 and 1 ng/µL of each drug in 0.01M HCl. Stock and working solutions of methylmaprotiline (MMP, internal standard) were prepared using 1 mg/mL in methanol and 2 ng/µL in 0.01M HCl, respectively. Working solutions were distributed into small aliquots and stored for up to 3 months at –20°C until use. All other reagents were of analytical or HPLC grade.

Instrumentation and chromatographic conditions

Analyses were performed on a Hewlett-Packard (Meyrin, Geneva, Switzerland) HP 5890 series II GC equipped with a splitless capillary and an electronic control pressure system. The GC was linked to a quadrupole HP 5972 MS operated in the electron impact mode. The MS conditions were as follows: ionizing electron energy, 50 eV; emission current, 50 µA; ion source temperature, approximately 180°C (heated by the interface); and GC–MS capillary direct interface, 280°C. Splitless injections of 3 µL were made into a fused-silica Optima 5 capillary column (15 m × 0.25-mm i.d., 0.25-µm film thickness) (Macherey-Nagel, Oensingen, Switzerland) with helium as the carrier gas. The column head pressure was set to maintain a constant flow with a pressure of 2 psi (14 KPa). The total flow was 50 mL/min and the septum purge was 3 mL/min. GC conditions

Table II. Statistical Data Concerning the Analysis of CIT, PAR, SER, and Their *N*-Demethylated Metabolites

	CIT	DCIT	DDCIT	PAR	SER	DSER
Calibration (*n* = 4)						
Range (ng/mL)	10–500	10–300	5–60	10–200	20–400	20–400
Slope: mean ± SD (CV)*	0.35 ± 0.02 (5)	11.2 ± 1.75 (16)	4.57 ± 1.09 (24)	0.94 ± 0.12 (13)	1.18 ± 0.05 (4)	1.37 ± 0.15 (11)
Coefficient of correlation: mean (range)	0.998 (0.997, 0.999)	0.998 (0.997, 0.999)	0.991 (0.988, 0.999)	0.995 (0.989, 0.998)	0.999 (0.997, 0.999)	0.995 (0.993, 0.999)
Recovery (*n* = 6)						
Concentration used (ng/mL)	20	20	10	20	30	30
Recovery (%): mean ± SD (CV)	112 ± 21 (19)	76 ± 8 (10)	46 ± 4 (9)	73 ± 13 (18)	81 ± 7 (9)	49 ± 6 (12)
Concentration used (ng/mL)	100	50	25	50	100	100
Recovery (%): mean ± SD (CV)	118 ± 16 (14)	84 ± 10 (12)	49 ± 6 (12)	80 ± 18 (22)	95 ± 13 (14)	66 ± 10 (15)
Concentration used (ng/ml)	300	100	40	150	300	300
Recovery (%): mean ± SD (CV)	91 ± 15 (16)	75 ± 11 (14)	39 ± 5 (12)	75 ± 7 (10)	75 ± 11 (14)	48 ± 7 (14)
Within-day variation (*n* = 8)						
Theoretical values (ng/mL)	20	20	10	20	30	30
Measured values (ng/mL): mean ± SD (CV)	20.8 ± 1.5 (7)	19.7 ± 1.7 (9)	9.6 ± 1 (10)	21.8 ± 3.0 (14)	31.4 ± 2.3 (7)	33.6 ± 2.6 (8)
Percentage of theory	104	99	96	109	105	112
Theoretical values (ng/mL)	100	50	25	50	100	100
Measured values (ng/mL): mean ± SD (CV)	90.1 ± 2.3 (3)	45.4 ± 1.7 (4)	25.5 ± 2 (8)	52.4 ± 2.2 (4)	93.7 ± 8.8 (9)	105 ± 11.9 (11)
Percentage of theory	90	91	102	105	94	105
Theoretical values (ng/mL)	300	100	40	150	300	300
Measured values (ng/mL): mean ± SD (CV)	283 ± 10.8 (4)	91.9 ± 5.1 (6)	40.9 ± 4.1 (10)	154 ± 7.7 (5)	299 ± 15.1 (5)	333 ± 32.5 (10)
Percentage of theory	94	92	102	102	100	111
Day-to-day variation (*n* = 7)						
Theoretical values (ng/mL)	20	20	10	20	30	30
Measured values (ng/mL): mean ± SD (CV)	21.5 ± 2.3 (11)	21.4 ± 1.9 (9)	10.5 ± 1.1 (10)	22.4 ± 3.4 (15)	34.3 ± 4.6 (13)	28.9 ± 3.7 (13)
Percentage of theory	107	107	105	112	114	96
Theoretical values (ng/mL)	100	50	25	50	100	100
Measured values (ng/mL): mean ± SD (CV)	89.1 ± 3.3 (4)	45.6 ± 4.2 (9)	26.4 ± 2.7 (10)	48.4 ± 5.3 (11)	95.4 ± 5.5 (6)	86.2 ± 6.7 (8)
Percentage of theory	89	91	106	97	95	86
Theoretical values (ng/mL)	300	100	40	150	300	300
Measured values (ng/mL): mean ± SD (CV)	284 ± 9.1 (3)	95 ± 6.5 (7)	44 ± 4.0 (9)	146 ± 12.7 (9)	292 ± 18.5 (6)	275 ± 20.7 (8)
Percentage of theory	94	95	111	97	97	92
Limit of quantitation (*n* = 8)						
Theoretical values (ng/mL)	2	0.5	0.5	2	1	0.5
Measured values (ng/mL): mean ± SD (CV)	2.14 ± 0.36 (17)	0.53 ± 0.06 (11)	0.47 ± 0.07 (16)	1.94 ± 0.19 (10)	0.96 ± 0.06 (6)	0.47 ± 0.08 (16)
Percentage of theory	107	106	94	97	96	94

*SD, standard deviation; CV, coefficient of variation (%).

were as follows: initial temperature, 160°C; initial time, 0.5 min; heating rate, 30°C/min until 260°C (final time 3.40 min); and injector temperature, 250°C. Analyses were performed in the selected-ion monitoring (SIM) mode with a dwell time of 50 ms for the ions at *m/z* 238 (DDCIT and DCIT), 274 (DSER and SER), 291 (MMP), 324 (CIT), and 425 (PAR).

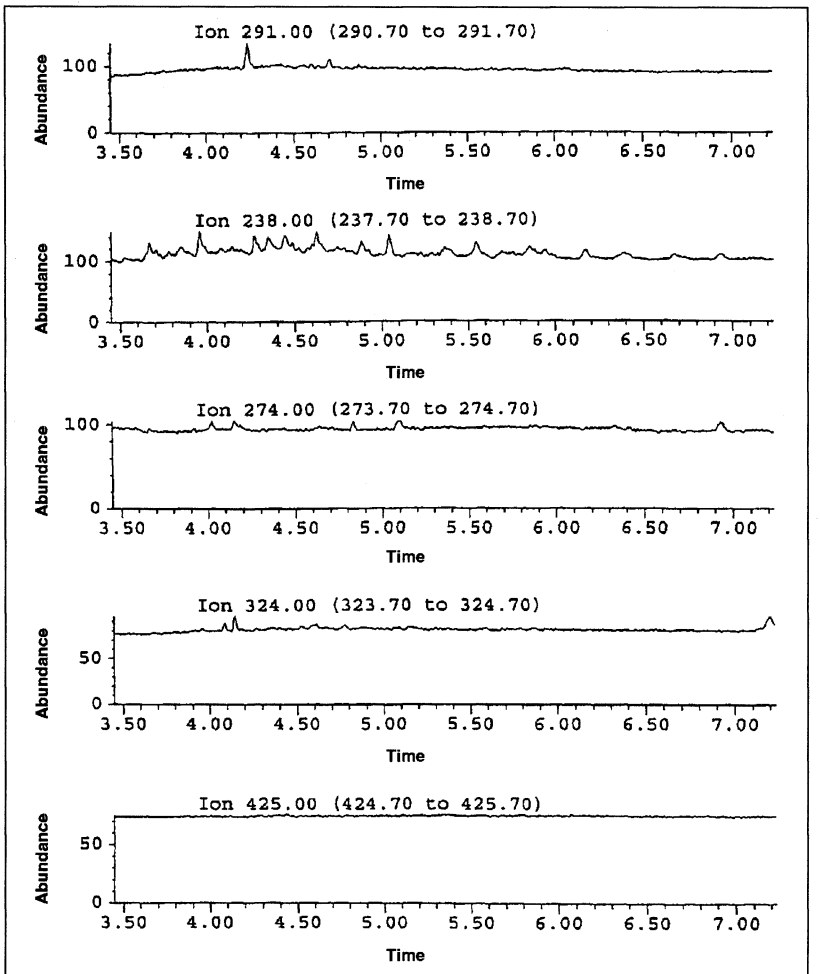

Figure 3. SIM tracing of 1 mL blank plasma.

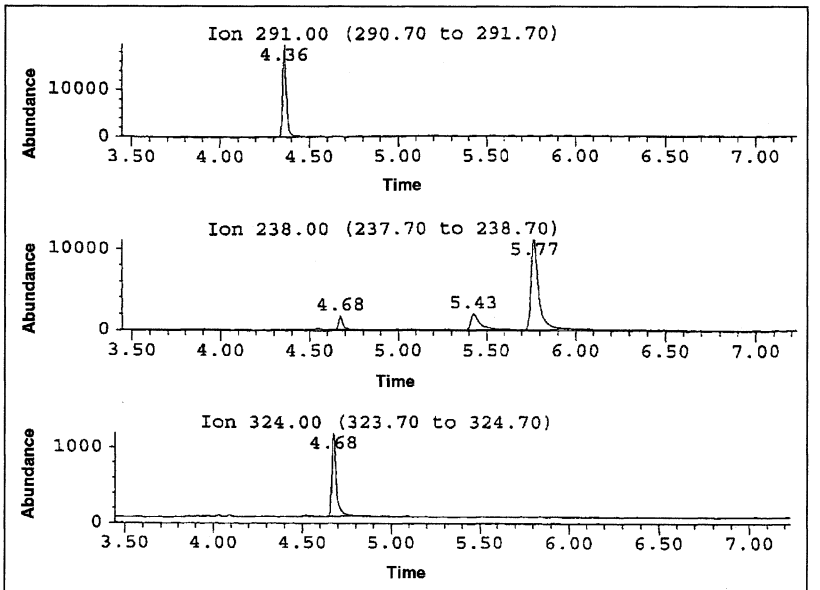

Figure 4. SIM tracing of 1 mL plasma from a patient receiving 20 mg/day CIT. CIT, ion 324, 4.68 min; DCIT, ion 238, 5.77 min; DDCIT ion 238, 5.43 min; MMP, ion 291, 4.36 min.

Extraction conditions

To a 1-mL volume of heparinized plasma sample were added 100 µL of MMP (internal standard, 2 ng/µL), 1 mL of 1M sodium carbonate buffer (pH 9.4), and 6 mL of *n*-heptane–ethylacetate (80:20, v/v). Extraction was performed on a rotary shaker for 15 min. After centrifugation (8 min, 3400 × *g*), the organic layer was transferred to another tube containing 1.2 mL 0.1M HCl. After shaking for 15 min and centrifugation, the aqueous phase was transferred to another tube containing 1 mL of 1M carbonate buffer (pH 9.4) and 150 µL of toluene–isoamylalcohol (85:15, v/v). After shaking for 15 min and centrifugation for 2 min, the solvent was transferred to injection vials and evaporated to dryness under a stream of nitrogen at 40°C.

Derivatization conditions

The residue was dissolved by thorough vortex mixing with 20 µL of *N*-methyl-bis(trifluoroacetamide) and left for 1 h at 60°C in a closed injection vial. The reagent was then evaporated to dryness under a stream of nitrogen at 40°C, reconstituted in 100 µL toluene–isoamylalcohol (85:15, v/v, thorough vortex mixing), and 3 µL was injected into the GC–MS system.

Results and Discussion

We recently described a GC–MS method for the simultaneous determination of FLV and the enantiomers of FLX and NFLX with (*S*)-(–)*N*-trifluoroacetylprolyl chloride as the derivatizing reagent (5). To our knowledge, this was the first published method which simultaneously measured the concentrations of two SSRIs. We first attempted to use the same reagent for the three remaining SSRIs without success. Apparently, there was no derivatization under our conditions (data not shown). After several trials with other reagents, we found that a good derivatization was obtained with *N*-methyl-bis(trifluoroacetamide). Table I lists the main ions in the mass spectra of CIT, SER, and PAR; of their *N*-demethylated pharmacologically active metabolites; and of MMP after derivatization with this reagent. The probable fragmentation pathways of the molecular cations of CIT, PAR, SER, and MMP are presented in Figure 2.

It should be mentioned that FLX, NFLX, and FLV (the other SSRIs not analyzed by the present method) are also readily derivatized with

N-methyl-bis(trifluoroacetamide) and elute at retention times which are different from those of CIT, PAR, SER, and their metabolites (data not shown). We did not include FLX, NFLX, and FLV in the validation steps of the present method because we were more interested in separating the enantiomers of the former drug, which is only possible with the use of a chiral derivatizing reagent. However, the method described in the present paper could allow the simultaneous determination of the five SSRIs presently on the market; that is, if one is not interested in measuring the enantiomers of FLX and NFLX separately. It should be mentioned that the present method and the method we previously described for FLX, NFLX, and FLV use the same extraction procedure.

Figure 3 shows the SIM tracing of a blank plasma. Figures 4–6 are examples of chromatograms obtained from the analysis of plasma samples drawn from patients receiving 20 mg/day of CIT, 40 mg/day of PAR, and 75 mg/day of SER, respectively. The measured concentrations of CIT, DCIT, DDCIT, PAR, SER, and DSER were 43, 24, 16, 74, 29, and 56 ng/mL, respectively.

Table 2 shows a summary of the statistical data on the analysis of CIT, PAR, SER, and their metabolites. In summary, the mean coefficients of correlation of the calibration curves obtained from four separate experiments were 0.998, 0.998, 0.991, 0.995, 0.999, and 0.995, respectively. It should be mentioned that no values are given for the intercepts because the option "force through the origin" was chosen for the calibration curves; with this option, better results were obtained for control plasma samples of low concentration (data not shown). Because pure standards of the derivatized compounds are not available, recovery was calculated by dividing the mean areas (n = 6) obtained after the complete extraction and derivatization procedure of plasmas containing low, medium, and high concentrations of the SSRIs by the mean areas obtained after direct derivatization of the same quantities of the pure standards. Recoveries were satisfactory for all compounds, ranging from 81 to 118% for the tertiary amines (CIT and MMP), from 73 to 95% for the secondary amines (DCIT, PAR, and SER), and from 39 to 66% for the primary amines (DDCIT and DSER). The variability of the assays for the intra- (n = 8) and the interday (n = 7) experiments measured at three concentrations for each substance, as assessed by the coefficients of variation, ranged from 3 to 11% for CIT and its metabolites, from 4 to 15% for PAR, and from 5 to 13% for SER and DSER. The percent theoretical concentrations, which represent the accuracy of the method, were all within ± 10% for CIT and its metabolites, within ± 9% for PAR, and within ± 12% for SER and DSER.

The limits of quantitation are defined as the concentrations for which the mean value of replicate determinations (n = 8) is within 20% of the actual value, the coefficient of variation less than 20%, and which gives a signal-to-noise ratio of at least 10. Limits of quantitation were 2 ng/mL for CIT and PAR, 1 ng/mL for SER, and 0.5 ng/mL for DCIT, DDCIT, and DSER.

The specificity of the assay was also evaluated. Samples (200 ng) of each of the following substances diluted in methanol were dried, derivatized, dried, reconstituted in 100 µL toluene–isoamylalcohol (85:15, v/v), and injected into the GC–MS: amitriptyline, nortriptyline, clomipramine, desmethylclomipramine, trimipramine, desmethyltrimipramine, maprotiline, methadone, mianserin, desmethylmianserin, clozapine, desmethylclozapine, imipramine, desmethylimipramine, fluoxetine, norfluoxetine, fluvoxamine, procyclidine, risperidone, and 9-hydroxy risperidone. No interferences were noted from these 20 psychotropic drugs. Likewise, no interferences were observed from endogenous compounds following the extraction of plasma samples from six

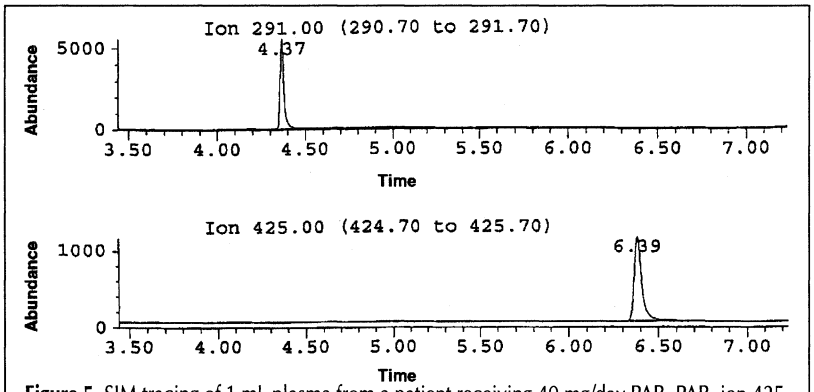

Figure 5. SIM tracing of 1 mL plasma from a patient receiving 40 mg/day PAR. PAR, ion 425, 6.39 min; MMP, ion 291, 4.37 min.

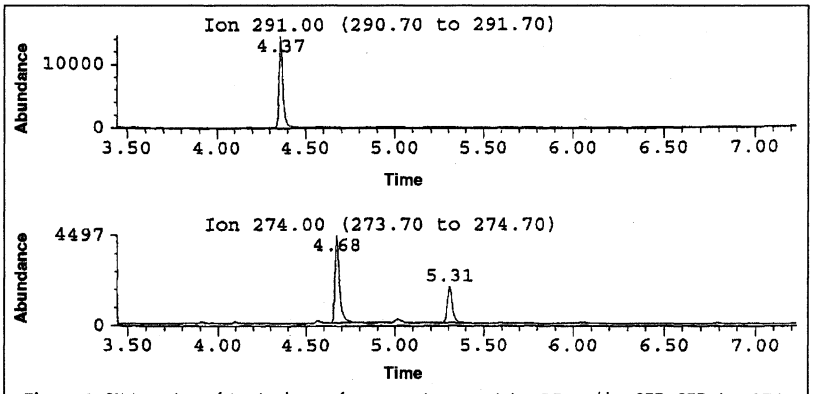

Figure 6. SIM tracing of 1 mL plasma from a patient receiving 75 mg/day SER. SER, ion 274, 5.31 min; DSER, ion 274, 4.68 min; MMP, ion 291, 4.37 min.

Table III. Relationships between the Concentrations of CIT, DCIT, and DDCIT as Measured by GC–MS and GC–NPD*

	GC–MS	*n*	*r*	r^2
CIT (ng/mL)	–1.772 + 0.89(GC–NPD)	60	0.991	0.982
DCIT (ng/mL)	–3.758 + 0.988(GC–NPD)	58	0.943	0.889
DDCIT (ng/mL)	–1.462 + 1.192(GC–NPD)	37	0.917	0.841

*There are unequal numbers of samples included in the statistical analysis because results that were below LOQ were eliminated.

different human controls who were not receiving any medication.

It should be noted that ions of high molecular weight or molecular ions were intentionally chosen in order to minimize potential interferences from other substances. Also, MMP, which was used as the internal standard, is not a metabolite of maprotiline and is not detected in patients receiving this drug (6). The stability of CIT, PAR, SER, and their metabolites was evaluated by analyzing spiked plasma samples stored at –20°C for different periods of time. No loss was noted after storage of up to 3 months. Finally, the stability of the derivatized forms of these three SSRIs with their metabolites was evaluated. No change was noted after storage of up to 3 days at room temperature (data not shown).

Before the development of the present method, the concentrations of CIT, DCIT, and DDCIT were measured in our laboratory using GC with a nitrogen-phosphorus detector (GC–NPD) after derivatization of the secondary and primary amines with trifluoroacetic anhydride (7). Sixty plasma samples which were sent to our laboratory for therapeutic drug monitoring of CIT using GC–NPD were reanalyzed using GC–MS. Table 3 shows the good correlations obtained between the two methods. It should be mentioned, however, that one value of DCIT was excluded from the statistical analysis because of a marked difference in the results between the two methods (142 ng/mL with GC–NPD and 30 ng/mL with GC–MS). We believe that the high DCIT concentration in the former method was caused by an unknown substance, probably a comedication, eluting at the same retention time.

Conclusion

This method, which is both sensitive and selective, allows the simultaneous quantification of CIT, PAR, SER, and their *N*-demethylated metabolites in plasma samples and can be used for single-dose pharmacokinetic studies. This procedure decreases the cost and time of analysis. It provides a good alternative analytical method for psychiatric patients who are often comedicated and also for patients who are medicated with two SSRIs (4). Finally, this method could probably be used for the simultaneous quantification of the five SSRIs on the market.

Acknowledgements

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