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Methods for the determination of seven selective serotonin reuptake inhibitors and three active metabolites in human serum using high-performance liquid chromatography and gas chromatography

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Abstract

This paper describes a set of simple and sensitive multiresidue methods for the determination of the specific serotonin reuptake inhibitors (SSRIs) used as antidepressant drugs, and some of their respective active metabolites in human serum. It involves liquid–liquid extraction procedures followed by gas chromatography coupled to nitrogen phosphorus detection or isocratic reversed-phase high-performance liquid chromatography combined with fluorescence detection (HPLC–FL), depending on the analytes. Extraction recoveries were between 71 and 96% for the eight SSRIs and their metabolites analysed by GC and between 41 and 77% for the two of them analysed by HPLC. Limits of detection (LODs) and limits of quantitation (LOQs) ranged, respectively, from 2.5 to 5 μg/l and from 10 to 20 μg/l. Intra-assay and inter-assay precision was studied at three and four concentration levels, respectively, and was less than 19% for all compounds. Accuracy was also satisfactory for all. An excellent linearity was observed from the LOQs up to 1000 μg/l for milnacipram and paroxetine and from each LOQ up to 400 mg/l for the other compounds. The performance of the methods described thus allows the therapeutic drug monitoring of the currently commercialised SSRIs.

Keywords: Serotonin; Specific serotonin reuptake inhibitors

1. Introduction

Antidepressant drugs are widely used for the treatment of a variety of depressive states and other psychiatric disorders. A new class of drugs, selective serotonin reuptake inhibitors (SSRIs), is more commonly used in clinical practice [1], which is why the analysis of SSRIs has become more important. The SSRIs are relatively nontoxic when taken alone, they are considered to be safe and well-tolerated drugs with minimal side effects and appear to have a wider therapeutic index than the tricyclics. However, in combination with other antidepressant and antipsychotic drugs, the SSRIs may interact with the co-administered drug to cause ineffective or toxic levels [2–5]. In addition, because some active metabolites, formed by N-demethylation particularly, contribute to the overall therapeutic effect of certain SSRIs, it is necessary to determine both the parent compounds and their major active metabolite [1,6].

Several chromatographic methods were developed for the determination of a few SSRIs in plasma and

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serum [7–9]. All the recent assays were based either on high-performance liquid chromatography (HPLC) with fluorometric or UV detection [10–12] or on gas chromatography (GC) with nitrogen phosphorus (NPD), electron capture (CED) or mass spectrometric (MS) detection [4,7,13–15]. Different extraction procedures have been used, the most common of which use liquid–liquid or solid-phase extraction [16–18] such as extraction with Extrelut columns [19].

As SSRIs differ widely in their chemical structure, analytical methods for their quantitative determination in biological matrices have been developed for each drug individually or for a few SSRIs [13,15]. Unfortunately, none allowed the simultaneous determination of the SSRIs commonly prescribed and their active metabolites such as desmethylcitalopram, norfluoxetine, desmethylsertraline. Indeed, such a method would be useful for economical reasons, but also in the case of suicide involving one of these SSRIs and their metabolite [8,9].

This paper presents a rapid and sensitive method for the quantitation of eight SSRIs and three active metabolites (citalopram, desmethylcitalopram, fluoxetine, milnacipram, norfluoxetine, paroxetine, fluvoxamine, sertraline, desmethylsertraline and venlafaxine), using either GC–NPD or isocratic reverse phase high-performance liquid chromatography combined with fluorescence detection (HPLC–FL) after derivatization.

2. Experimental

2.1. Reagents and materials

Milnacipram and methylmilnacipram (internal standard, I.S.) were obtained from IRPF/CDPF (Labege, France). Citalopram and desmethylcitalopram were purchased from Lundbeck (Copenhagen, Denmark). Sertraline and desmethylsertraline were purchased from Pfizer (Illertissen, Germany), venlafaxine from Lederle (Pearl River, NY, USA), fluoxetine from Lilly (Paris, France) and norfluoxetine from RBI (Natick, MA, USA). Paroxetine was from Smithkline-Beecham (Mayenne, France), fluvoxamine from Solvay-Pharma (Suresnes, France), maprotiline (I.S. for paroxetine) from Ciba-Geigy (Huningue, France) and protryptiline (I.S. for GC analysis) was obtained from Merck (Darmstadt, Germany). Dansyl chloride was obtained from Sigma (Paris, France).

Toluene (Chromanorm grade), *n*-heptane (Pestinorm grade), sodium acetate, sodium hydrogen carbonate, sodium hydroxide, acetone, acetic acid, isoamyl alcohol (Normapur grade) and sodium carbonate were purchased from Prolabo (Paris, France). All were of chromatographic purity. HPLC-grade acetonitrile and methanol were obtained from Merck.

The carbonate–bicarbonate buffer (pH 9.7) was prepared by mixing a solution of anhydrous sodium carbonate (0.2 *M*) and a solution of sodium hydrogen carbonate (0.2 *M*) and adjusting the pH to 9.7.

2.2. Preparation of standards

Stock solutions of citalopram, desmethylcitalopram, fluvoxamine, paroxetine, sertraline, desmethylsertraline, venlafaxine, fluoxetine, norfluoxetine and milnacipram were prepared at 1.0 g/l of each drug in methanol. Working solutions were prepared by appropriate dilution of stock solutions with methanol, except for milnacipram and paroxetine, which were diluted with deionised water. For the GC method, two pooled SSRI working solutions (1 and 10 mg/l) were prepared by mixing appropriate amounts of stock solutions: one containing citalopram, desmethylcitalopram, fluvoxamine, paroxetine, sertraline, desmethylsertraline, venlafaxine and the other containing fluoxetine and norfluoxetine. The stock and working solutions of protryptiline (I.S. for GC analysis) were prepared in methanol at 1.0 g/l and 2.0 mg/l, respectively. Stock and working solutions of maprotiline (I.S. for paroxetine) and methylmilnacipram (I.S. for milnacipram) were prepared at 1 g/l in methanol and 100 μg/l in deionised water, respectively. All stock and working solutions were stored at +4°C for a maximum of 1 month.

2.3. Preparation of calibration curves

Routine daily calibration curves were prepared for each analytical batch in drug-free serum. For the GC method, appropriate volumes of the pooled working solution and 100 μl of a 2 mg/l protryptiline (I.S.)

solution were added to the tubes containing 1 ml serum. Final concentrations were 20, 50, 100, 200, and 400 μg/l. For the HPLC method, appropriate volumes of the working solution of milnacipram or paroxetine and 500 μl of a 100 μg/l I.S. solution were added in each test tube containing 1 ml serum. Final concentrations were 5, 25, 50, 100, 500, and 1000 μg/l. An extract of blank serum was also prepared for every calibration.

2.4. Gas chromatography nitrogen phosphorus detection

A Varian 3400 gas chromatograph (les Ulis, France), equipped with a nitrogen phosphorus detector (NPD) and a glass-stem (Ros) manual injector was used for the analysis. Helium was used as carrier gas at a flow-rate of 1.4 ml/min, and as make-up gas at a flow-rate of 25 ml/min. Detector, air and hydrogen flow-rates were set at 175 and 1.4 ml/min, respectively. The injector port and detector were maintained at 300°C. The analytical column used was a PTE 5, 30 m×0.25 mm I.D., coated with a 5% biphenyl–95% dimethylsiloxane stationary phase of 0.25 μm thickness (Supelco, St-Quentin-Fallavier, France). Different temperature programs were used for two groups of molecules: for fluoxetine and norfluoxetine, the starting temperature was 160°C and, after 1 min, the temperature was raised at 5°C/min to 200°C and then at 20°C/min up to 280°C, maintained for 2 min. The total chromatographic time, including re-equilibration, was 17 min. For citalopram, desmethylcitalopram, fluvoxamine, paroxetine, sertraline, desmethylsertraline and venlafaxine, the initial oven temperature was 200°C and was ramped at 5°C/min to 250°C, then at 5°C/min to 280°C and maintained for 1 min. The total chromatographic time, including equilibration, was also 17 min. Data acquisition, calculation and quantitation were performed using the PE Nelson-Turbochrom (version 2.1) software (Cuperano, CA, USA).

2.5. High-performance liquid chromatography

For the determination of milnacipram and paroxetine, the HPLC system used consisted of a Waters 6000 A pump (Waters, Milford, MA, USA) connected to a 7125 Rheodyne® injector (Cocati, CA, USA). Separation was performed on a Hypersil® ODS, 150×4.6 mm I.D. (3 μm dp) column (Touzart et Matignon, les Ulis, France).

The isocratic mobile phases consisted of two different mixtures of sodium acetate solution (0.005 *M*, pH 4.5) and methanol: for milnacipram 30:70 (v/v) and for paroxetine 16:84 (v/v). The sodium acetate solution was prepared by diluting sodium acetate solution (0.1 *M*) in deionised water and adjusting the pH to 4.5 with glacial acetic acid. The mobile phase was filtered through a 0.45 μm filter prior to use. The mobile phase flow-rate was 1.0 ml/min. The effluent was continuously monitored using an F1000 fluorescence detector (Hitachi, Kyoto, Japan) set to 340 nm (excitation) and 520 nm (emission) wavelengths. Data acquisition was performed using a 3390 A Hewlett-Packard integrator.

2.6. Extraction procedures

2.6.1. Prior to GC

To 1 ml serum, 100 μl of a 2 mg/l protryptiline (I.S.) solution, 1 ml of 0.25 *M* NaOH and 7 ml of the extracting solvent heptane–isoamyl alcohol 98.5:1.5 (v/v) was added. The mixture was shaken for 15 min, centrifuged at 3000 rev./min (2600×*g* at 25°C) for 5 min and the aqueous layer was discarded. To the organic phase, 1 ml of 0.1 *N* HCl was added. The mixture was shaken for 15 min and centrifuged (2600×*g*, 25°C) for 5 min. The organic phase was removed, 1 ml of carbonate–bicarbonate buffer (pH 9.7) and 50 μl of a toluene–isoamyl alcohol 98.5:1.5 (v/v) mixture were added to the remaining aqueous phase. The tubes were shaken for 15 min and centrifuged (2600×*g*) for 5 min. The final aqueous layer was aspirated and 3 μl of the organic supernatant phase were injected onto the GC column.

2.6.2. Prior to HPLC

To 1 ml serum, 500 μl of a 100 μg/l solution of I.S. (maprotiline for paroxetine, methylmilnacipram for milnacipram), 250 μl phosphate buffer (0.12 *M*, pH 12) and 4 ml toluene were added. The mixture was shaken for 15 min and centrifuged at 2600×*g* for 5 min. The aqueous phase was removed and the organic phase evaporated to dryness at 37°C. To the residue, 50 μl acetone, 25 μl sodium hydrogen carbonate (0.1 *M*; pH 4.5) and 10 μl dansylchloride

(1 g/l) were added. The mixture was vortex-mixed for 30 s and heated at 55°C for 1 min. After 15 min at room temperature, 75 μl of L-proline were added, the mixture was vortex-mixed and incubated 5 min at room temperature. Then, 2.5 ml of toluene and 250 μl of deionised water were added, mixed for 15 min and centrifuged at 2600×*g*. The organic phase was transferred and evaporated to dryness at 37°C under a gentle stream of nitrogen. The extract was redissolved in 100 μl mobile phase and 50 μl were injected onto the HPLC column.

2.7. Validation of the methods

Recovery was determined in triplicate at three and two concentration levels for GC and HPLC, respectively, by comparing the analyte/I.S. peak area ratios obtained with those of unextracted solutions.

The intra-assay precision was assessed at three concentration levels by extraction and analysis on the same day of five fortified serum samples for each level. The inter-assay precision was assessed by analysing each day for 5 days ($n=5$) a set of four concentration levels. The accuracy was determined by subtracting the measured concentration from its theoretical value and expressed as the mean relative error (MRE) of the difference from theoretical. The limit of detection (LOD) was determined as the lowest concentration giving a response of three times the average of the baseline noise defined from three control samples. The limit of quantitation (LOQ) was determined as the lowest concentration of a given SSRI or metabolite giving a response that could be quantified with both intra-assay relative standard deviation (RSD) and MRE lower than 20%. The linearity of the method for each compound was checked by preparing calibration standards (five replicates) at six different concentrations, ranging from 20 to 400 ng/ml for the GC method and from 5 to 1000 ng/ml for the HPLC methods, by addition of known amounts of each drug to drug-free human serum. The calibration curves of the SSRIs-to-I.S. peak-area ratios versus theoretical analyte concentration were obtained by least-square quadratic regression and linear regression for the GC and HPLC methods, respectively. Routine calibration curves were obtained daily by analysing drug-free serum samples fortified with each analyte.

3. Results and discussion

3.1. Chromatography

Good chromatographic results were obtained from the extracts with the four methods using two different chromatographic and with two different detection techniques. Figs. 1 and 2 show representative GC chromatograms of extracted serum samples for the drug groups for each method. Alkaline extraction (pH=9) followed by an acidic purification step (pH=3) provided extracts free of contaminants in the areas corresponding to the retention time of the 10 compounds (Fig. 1). A temperature program was created for six SSRIs which were separated into two calibration groups due to incomplete resolution; group 1: citalopram, desmethylcitalopram, venlafaxine; group 2: sertraline, desmethylsertraline and fluvoxamine. The separation of norfluoxetine from fluoxetine required a slightly different temperature program.

The nitrogen-containing structures of citalopram, desmethylcitalopram, fluoxetine, norfluoxetine, fluvoxamine, paroxetine, sertraline, desmethylsertraline and venlafaxine are responsible for the high sensitivity obtained using a nitrogen phosphorus detector (NPD), as well as for the minimisation of interferences.

Representative HPLC chromatograms of extracted human serum samples are shown in Fig. 2a–c. Despite the background noise at the excitation ($\lambda=$ 340 nm) and emission ($\lambda=520$ nm) wavelengths chosen for fluorescence detection, no interferences were detected for milnacipram and paroxetine. These compounds were eluted at 11.1 and 7.2 min, respectively (Fig. 2a–c).

3.2. Sample extraction

Liquid–liquid extraction was used for both the GC and HPLC methods, because of its high efficiency, selectivity and simplicity. Despite differences in chemical structure, eight SSRIs could be assayed by GC, while two others required HPLC separation. N-desmethylated metabolites of some of the compounds, also SSRIs, also requires that parent compounds and their active metabolites be resolved. For the GC procedure, the polarity of the extraction

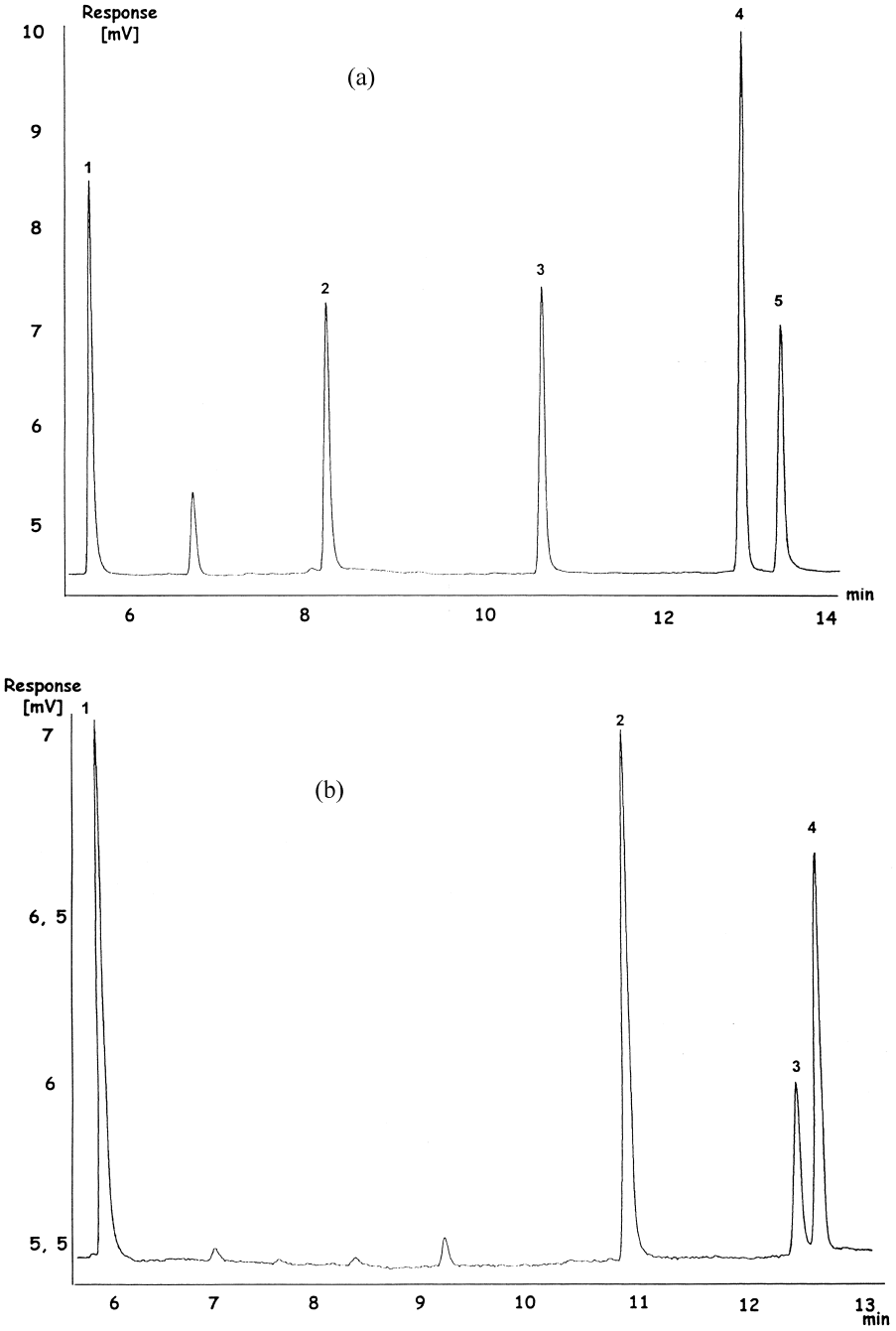

Fig. 1. Representative GC chromatograms of (a) serum spiked with 200 ng protryptiline (I.S.) (3, retention time: 10.7 min) and 200 μg/l each: fluoxetine (1, retention time: 5.8 min), venlafaxine (2, retention time: 8.4 min), citalopram (4, retention time: 12.9 min), desmethylcitalopram (5, retention time: 13.3 min). (b) Serum spiked with 200 ng protryptiline (I.S.) (2, retention time: 10.8 min) and 200 μg/l: fluvoxamine (1, retention time: 5.9 min), desmethylsertraline (3, retention time: 12.31 min), sertraline (4, retention time: 12.5 min). (c) Control serum spiked with 200 ng protryptiline (I.S.) (3, retention time: 13.7 min) and 400 μg/l norfluoxetine (1, retention time: 9.7 min), fluoxetine (2, retention time: 9.9 min). (d) Clinical serum sample spiked with 200 ng protryptiline (I.S.) (4, retention time: 13.3 min) and containing norfluoxetine 75 μg/l (1, retention time: 9.1 min), fluoxetine 207 μg/l (2, retention time: 9.32 min).

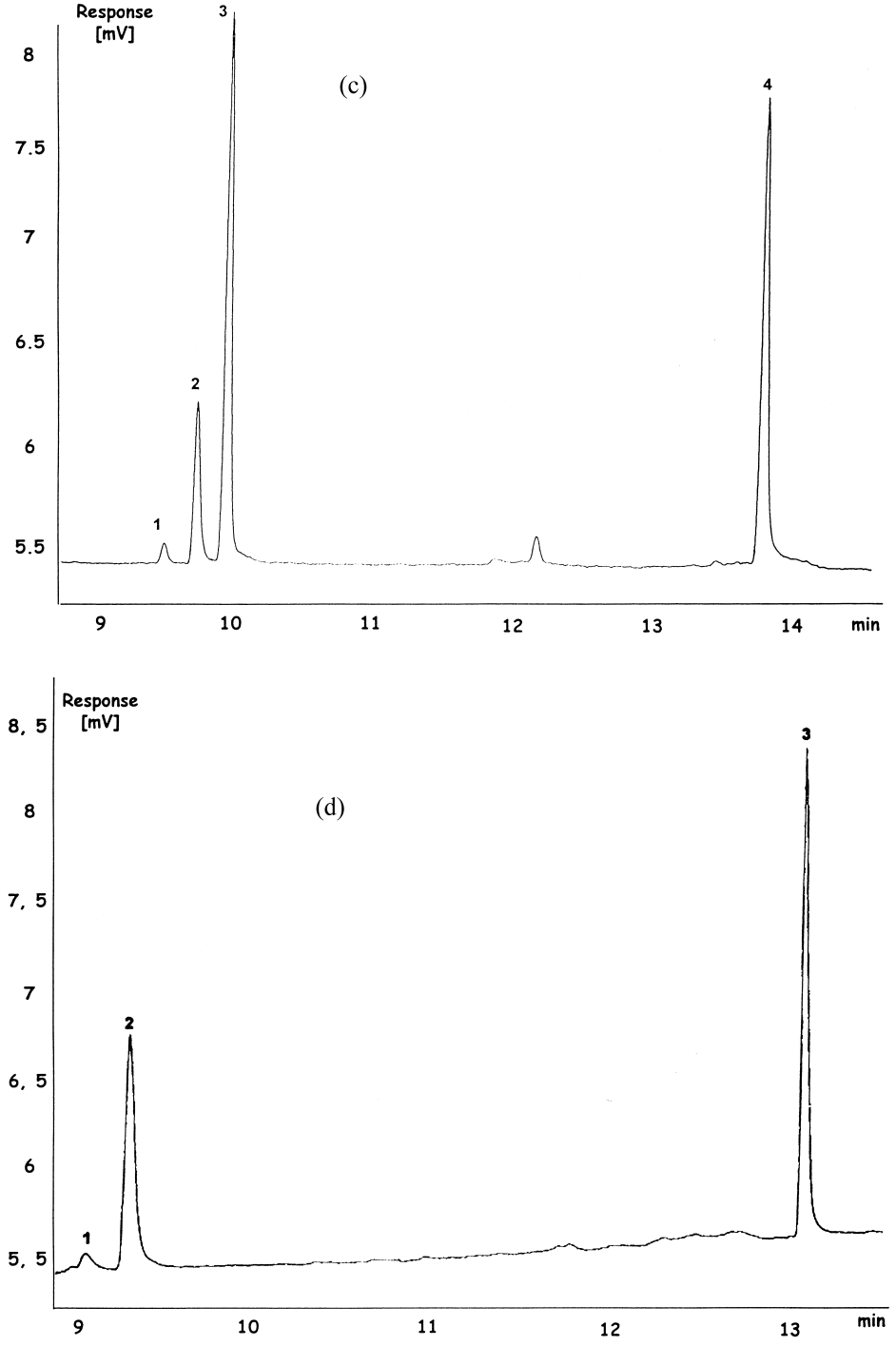

Fig. 1. (*continued*)

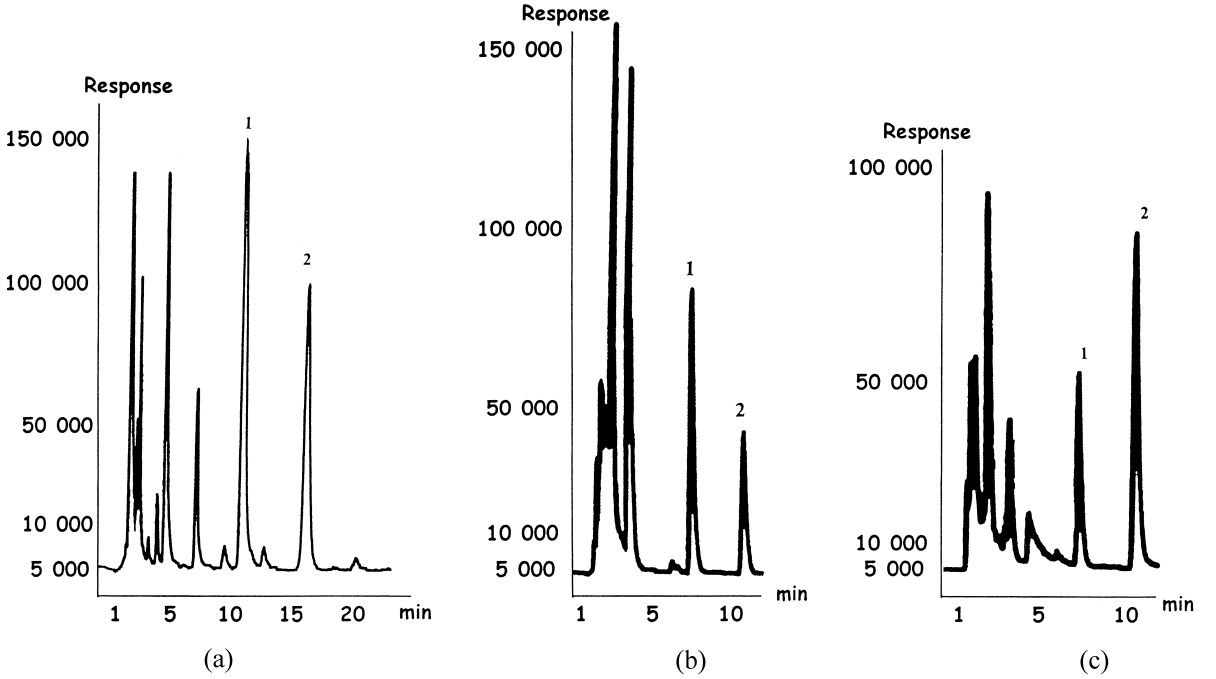

Fig. 2. Representative chromatograms of (a) serum spiked with 100 μg/l milnacipram (1, retention time: 11.1 min) and 50 ng methylmilnacipram (I.S.) (2, retention time: 16.4 min). (b) Serum spiked with 100 μg/l paroxetine (1, retention time: 7.25 min) and 50 ng maprotiline (I.S.) (2, retention time: 10.3 min). (c) Clinical serum sample containing 27 μg/l paroxetine (1, retention time: 7.3 min) and 50 ng (I.S.) (2, retention time: 16.4 min).

solvent, i.e. the proportion of isoamyl alcohol in the mixture with hexane has been shown to be the most important variable influencing extraction [20]. In the present and published studies [21], the best amount of isoamyl alcohol was found to be 1.5%.

The extraction recoveries (Tables 1 and 2) were higher than 71% for all compounds at each concentration, except for milnacipram, for which a recovery between 40 and 50% was measured. This relatively low recovery for milnacipram can be explained by the extraction procedure used, which was first developed for paroxetine. We did not notice any significant differences between the extraction recoveries of any metabolites compared to its parent compound.

The chemical structures of milnacipram and paroxetine are unrelated and sodium acetate solution

Table 1
Extraction recovery (%) of the five SSRIs and three metabolites in serum analysed by GC–NPD (three replicates at each concentration)

Compound	Concentration (μg/l)		
	10 Mean±SD	20 Mean±SD	400 Mean±SD
Fluoxetine	76.5±8.1	89.6±3.1	96.0±3.4
Norfluoxetine	78.2±3.1	93.2±7.2	93.5±3.3
Fluvoxamine	71.1±11.8	80.1±2.6	93.0±1.3
Citalopram	85.5±10.8	95.6±5.4	91.2±2.6
Desmethylcitalopram	85.7±7.4	86.8±7.7	92.3±4.1
Sertraline	71.4±5.6	85.1±4.7	80.5±2.2
Desmethylsertraline	87.5±5.1	88.5±6.0	88.7±1.9
Venlafaxine	78.3±3.4	85.6±2.8	94.0±0.9

Table 2
Extraction recovery (%) of milnacipram and paroxetine from serum as analysed by HPLC–FL (three replicates at each concentration)

Compound	Concentration (μg/l)	
	5 Mean±SD	1000 Mean±SD
Milnacipram	40.6±6.4	59.8±1.5
Paroxetine	76.9±4.1	75.4±7.1

Table 3
Intra-assay accuracy and precision for the quantitation of the five SSRIs and three metabolites in human serum using GC–NPD

Compound	Concentration (μg/l)	Mean	RSD (%)	MRE (%)
Fluoxetine	20	19.6	3.3	−2.0
	100	99.3	2.4	−0.7
	400	396.0	2.1	−1.0
Norfluoxetine	20	22.6	7.6	13.0
	100	100.3	1.8	0.3
	400	402.7	1.7	0.7
Fluvoxamine	20	18.9	1.9	−5.5
	100	99.0	1.0	−1.0
	400	403.6	2.3	0.9
Citalopram	20	18.6	3.3	−7.0
	100	101.6	0.6	1.6
	400	406.9	1.6	1.7
Desmethylcitalopram	20	19.2	8.7	−4.0
	100	100.7	1.1	0.7
	400	399.2	0.8	−0.2
Sertraline	20	18.2	7.8	−9.0
	100	100.4	1.3	0.4
	400	401.5	2.2	0.4
Desmethylsertraline	20	19.2	12.5	−4.0
	100	100.8	1.1	0.8
	400	398.8	1.1	−0.3
Venlafaxine	20	19.3	4.8	−3.5
	100	100.4	2.0	0.4
	400	403.6	0.8	0.9

chloride was shown to be the best method in terms of sensitivity for the determination of these two drugs [11].

The absence of interferences from the matrix was further confirmed by the daily use of the method with many different samples. Moreover, blank serum samples were included in all the calibration sets.

3.3. Validation

The present methods are repeatable for all the compounds, as shown by the intra-assay precision values (generally, RSD<16%); (Tables 3 and 4). The inter-assay precision for all compounds was also good at concentrations above each LOQ, with RSD values lower than 20% (Tables 5 and 6). The intra- and inter-assay MRE was always less than 12.5%, except for paroxetine and milnacipram at 5 ng/ml (Tables 3–6). The respective LOD and LOQ were 10 and 20 ng/ml for citalopram, desmethylcitalopram, fluoxetine, norfluoxetine, fluvoxamine, paroxetine, sertraline, desmethylsertraline and venlafaxine. For both milnacipram and paroxetine, they were 2.5 and 5 ng/ml, respectively. These LOD and LOQ values represent an improvement with respect to previous methods (LOQ ranging from 2 to 50 ng/ml) [11–13]. Few of them were more sensitive than the present method, while they were limited to the

Table 4
Intra-assay accuracy and precision for the quantitation of milnacipram and paroxetine in human serum using HPLC–FL

Compound	Concentration (μg/l)	Mean	RSD (%)	MRE (%)
Milnacipram	5	5.3	16.0	6.0
	50	56.0	2.2	12.0
	1000	1051.8	2.2	5.2
Paroxetine	5	5.8	10.5	16.0
	50	56.2	5.8	12.4
	1000	1000.6	4.3	0.0

Table 5
Inter-assay accuracy and precision for the quantitation of five SSRIs and three metabolites in human serum using GC–NPD

Compound	Concentration (μg/l)	Mean	RSD (%)	MRE (%)
Fluoxetine	20	19.9	11.3	−0.5
	50	49.0	5.0	−2.0
	100	97.1	4.2	−2.9
	400	399.7	0.1	−0.1
Norfluoxetine	20	22.5	14.0	12.5
	50	52.3	7.6	4.6
	100	96.5	5.8	−3.5
	400	399.8	0.1	−0.0
Fluvoxamine	20	20.3	12.0	1.5
	50	48.4	3.5	−3.2
	100	99.4	4.7	−0.6
	400	399.9	0.1	−0.0
Citalopram	20	18.0	10.0	−10
	50	52.2	3.0	4.4
	100	101.6	6.5	1.6
	400	400.1	0.1	0.0
Desmethylcitalopram	20	18.5	6.6	−7.5
	50	50.6	3.3	1.2
	100	99.8	6.7	−0.2
	400	400.0	0.2	0
Sertraline	20	18.3	11.7	−8.5
	50	53.4	6.0	6.8
	100	97.9	5.2	−2.1
	400	400.0	0.1	0
Desmethylsertraline	20	20.7	18.3	3.5
	50	51.4	9.3	2.8
	100	98.8	5.2	−1.2
	400	399.9	0.2	0
Venlafaxine	20	18.3	14.0	−8.5
	50	51.8	6.5	3.6
	100	101.7	4.7	1.7
	400	400.2	0.1	0.1

determination of only one SSRI and its main metabolites. Furthermore, the criteria chosen to define the LOQ were not always clearly defined. The only sensitive procedure allowing the simultaneous determination of fluoxetine, norfluoxetine, citalopram, desmethylcitalopram and also didesmethylcitalopram required derivatization and mass spectrometry [7].

Although no therapeutic window has been clearly defined for SSRIs, the most recent clinical studies published showed that the optimal plasma concen-

Table 6
Inter-assay accuracy and precision for the quantitation of milnacipram and paroxetine in human serum, using HPLC–FL

Compound	Concentration (μg/l)	Mean	RSD (%)	MRE (%)
Milnacipram	5	6.3	20.4	−26.0
	50	49.8	6.9	−0.4
	500	510.0	4.0	2.0
	1000	994.4	1.0	−0.6
Paroxetine	5	6.3	18.6	26.0
	50	48.4	8.1	3.2
	500	499.8	3.6	0.0
	1000	1000.5	0.9	0.1

trations mostly ranged between 50 and 400 μg/l [6,21]. Indeed, the relatively low LOQ (20 ng/ml) found herein for citalopram, desmethylcitalopram, fluoxetine, norfluoxetine, fluvoxamine, paroxetine, sertraline, desmethylsertraline and venlafaxine is suitable for their therapeutic drug monitoring.

The linearity of the GC method was satisfactory over the range 20 to 400 μg/l. The calibration curves obtained using quadratic regression gave the best correlation coefficients (r^2>0.998; n=5). The calibration curves of milnacipram and paroxetine obtained using the HPLC procedure were linear over the range of 5 to 1000 μg/l, also with excellent correlation coefficients (r^2>0.999; n=5).

4. Conclusion

The assays described herein allowed the determination of seven SSRIs and three metabolites with satisfactory recoveries and LOQs. The good specificity of these methods allow toxicological screening as well as therapeutic drug monitoring of several SSRIs available commercially.

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