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HPLC analysis of the novel antipsychotic drug quetiapine in human plasma

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Abstract

A precise and feasible high-performance liquid chromatographic (HPLC) method for the analysis of the novel antipsychotic drug quetiapine in plasma has been developed. The analysis was carried out on a C8 (150 × 4.6 mm i.d., 5 μm) reversed-phase column, using a mixture of acetonitrile, methanol and pH 1.9 phosphate buffer as the mobile phase; triprolidine was used as the internal standard. Careful pretreatment of the biological samples was implemented by means of solid-phase extraction (SPE). A good linearity was found in the 4–400 ng ml^{-1} quetiapine plasma concentration range. The application to some plasma samples of patients treated with Seroquel® tablets gave satisfactory results. The accuracy was good (quetiapine mean recovery = 92%), as well as the precision (mean RSD = 3.3%). The method seems to be suitable for the clinical monitoring of patients treated with quetiapine.

Keywords: HPLC analysis; Antipsychotic drug; Quetiapine; Solid-phase extraction

1. Introduction

The treatment of schizophrenia has made great strides with the introduction of 'atypical' antipsychotic drugs, as opposed to 'classical' antipsychotics such as chlorpromazine and haloperidol [1]; in fact, atypical antipsychotics have higher efficacy and tolerability, and have notably improved the quality of life of many patients. One of the most recently introduced atypical antipsychotics is quetiapine (2-(2-[4-(dibenzo[*b*,*f*]thiazepin-11yl)piperazin-1-yl]ethoxy)ethanol, Fig. 1a), a drug belonging to the group of the dibenzothiazepines and structurally similar to clozapine, the first atypical antipsychotic (Fig. 1b).

Quetiapine is mainly metabolised in the liver [2], and hepatic metabolism accounts for the formation of at least 11 metabolites [3].

Quetiapine has favourable effects on both the positive (e.g. hallucinations and delusions) and the negative (e.g. poverty of speech, flat affectivity and apathy) symptoms of schizophrenia [4] with clinical efficacy comparable to those of chlorproma-

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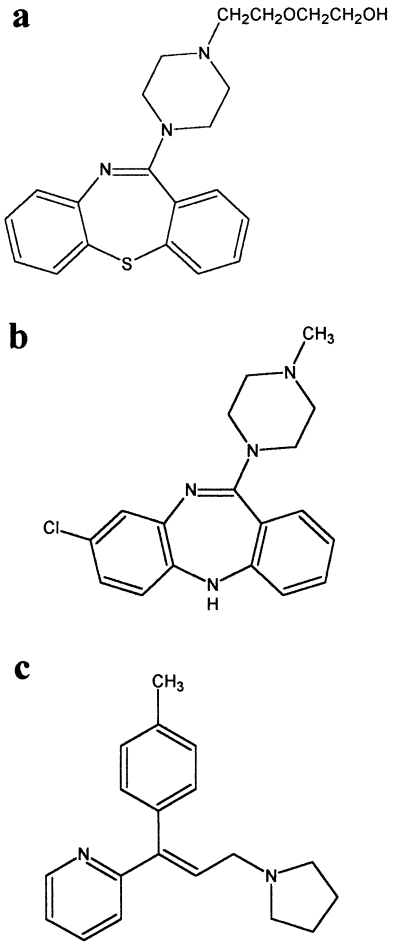

Fig. 1. Chemical structures of quetiapine (a), clozapine (b) and the I.S. triprolidine (c).

zine, haloperidol [5,6] and risperidone [7]. Quetiapine reduces positive symptoms at doses ranging from 150 to 750 mg per day and negative symptoms at doses equal to or higher than 300 mg per day [8]. The plasma quetiapine concentrations reported [9]for patients receiving 150 mg per day of quetiapine are in the 25–75 ng ml^{-1} range (samples taken 12 h after the last administration). Quetiapine tolerability is higher than that of classical neuroleptics: it causes an incidence of extrapyramidal symptoms much lower than that of haloperidol [10], and it does not induce reproductive/hormonal side effects [11].

Moreover, quetiapine does not cause significant changes in hematological parameters [12] such as agranulocytosis which is the most worrysome side effect associated with clozapine therapy [13]. All these advantages can be explained by the peculiar affinity spectrum of quetiapine for several neurotransmitter systems [14]. Recent studies suggest that quetiapine could be beneficial for the treatment of obsessive-compulsive disorders when coadministered with SSRI (selective serotonin reuptake inhibitor) antidepressants [15]. The main side effects of quetiapine, even with overdosing, are hypotension, tachicardia and somnolence [16], and this high degree of safety in the treatment leads to better *compliance* and higher efficacy of therapy with quetiapine [17], especially for adolescents [18,19], the elderly and those populations particularly susceptible to the adverse effects of drugs [20].

Up until now, however, the association between plasma quetiapine concentration and clinical response has not been sufficiently studied [3]; thus, new investigations should be conducted in this field, and new analytical methods should be developed to carry out a reliable drug monitoring of quetiapine [21].

To our knowledge, only three papers regarding the determination of quetiapine are present in the literature, and they report the analysis of the drug in biological fluids.

The first paper [22] describes two analytical methods for the quantitation of quetiapine and one metabolite in plasma, one based on HPLC with UV detection (at 250 nm) and the other on gas chromatography–mass spectrometry. Sample pretreatment was carried out by SPE (solid phase extraction) procedure on phenyl cartridges.

The second paper uses HPLC with UV detection (at 225 nm) for quetiapine analysis and electrochemical detection for the determination of two of its metabolites [9]. Quetiapine was extracted from samples by means of liquid–liquid extraction with ethyl acetate.

Both HPLC methods [9,22] use a mobile phase at neutral pH, thus an high percentage of organic modifiers is needed to elute the basic analytes within reasonable run times.

The third paper [23] regards the analysis of quetiapine alone in postmortem specimens by gas chromatography with a nitrogen–phosphorus de-

tector, after a complicated three-step liquid–liquid extraction with *n*-butylchloride, hydrochloric acid and 2-methylbutane.

Of course, both gaschromatographic methods [22,23] have the drawback of needing quetiapine derivatisation before analysis.

No analytical paper is available for the quality control of pharmaceutical formulations containing quetiapine; our research team has recently developed two fast and feasible analytical methods based on spectrophotometry and capillary electrophoresis for the analysis of quetiapine in commercial tablets [24].

Within the field of the research on the therapeutic monitoring of atypical antipsychotics, we have developed some original methods for the determination of clozapine [25–27] and olanzapine [28–30] in human plasma. In this paper a reliable analytical method for the analysis of the novel antipsychotic quetiapine in the plasma of patients is described; it uses HPLC with UV detection at 254 nm and is more precise and feasible than the other HPLC methods available [9], mostly due to an original SPE procedure of quetiapine extraction from plasma, which grants very good extraction yields. Preliminary results of this investigation were presented at the 2nd International Symposium on Separations in the Biosciences [31].

2. Experimental

2.1. Chemicals

Quetiapine was kindly provided by AstraZeneca (Macclesfield, UK). Triprolidine (Fig. 1c) used as the internal standard (I.S.) was purchased from Sigma Chemicals Ltd. (St. Louis, USA).

Potassium dihydrogen phosphate, sodium carbonate, 80% (m/m) phosphoric acid and triethylamine, all pure for analysis, methanol and acetonitrile for HPLC were from Carlo Erba (Milan, Italy).

Ultrapure water (18.2 MΩ cm) was obtained by means of a Millipore (Bedford, MA, USA) MilliQ apparatus.

2.2. Apparatus and chromatographic conditions

A JASCO (Tokyo, Japan) Uvidec-610 double-beam spectrophotometer was used for preliminary assays.

A JASCO PU-980 chromatographic pump connected to a JASCO UV-975 spectrophotometric detector was used for the chromatographic assays.

The analyses were carried out on a Varian (Harbor City, CA, USA) ResElut C18 reversed phase column (150 × 4.6 mm i.d., 5 μm) using a mobile phase composed of pH 1.9, 15.4 mM phosphate buffer containing 11.5 mM triethylamine, acetonitrile and methanol (72/12/16, v/v/v, pH* = 2.5) and flowing at a 1 ml min^{-1} rate. The assays were carried out at room temperature (25 ± 3 °C).

Samples were injected by means of a 20 μl loop and the detector was set at $\lambda = 254$ nm.

Data were collected and analysed by means of Star Chromatography software running on an IBM computer equipped with a 40486 processor.

2.3. Solutions

Stock solutions of quetiapine fumarate and triprolidine (1 mg ml^{-1}) were prepared in methanol. All standard solutions were prepared by diluting the stock solutions with the mobile phase.

The pH 10.3, 100 mM carbonate buffer solution was obtained by dissolving a suitable amount of sodium carbonate in water.

2.4. Human plasma sampling

The assays were carried out on plasma samples from schizophrenic patients of the Psychiatric Clinic of the University of Bologna drawn 12 h after the last administration.

The samples were drawn into test tubes containing EDTA as an anticoagulant and centrifuged at 1400 × *g* for 15 min. The supernatant plasma was transferred into test tubes and frozen at −20 °C until analysis, usually within 2 weeks. This procedure was also used to separate plasma from the blood of healthy volunteers ('blank' plasma).

2.5. Stability of plasma samples

From preliminary assays, quetiapine resulted to be stable in plasma. In fact, the same biological samples containing quetiapine were analysed by HPLC several times at different time intervals, even up to 2 months apart and after freezing and thawing, and no substantial difference in the analytical results was found.

2.6. Sample pretreatment: SPE procedure

For the SPE procedure Oasis HLB (Hydrophilic–Lipophilic Balance) cartridges (30 mg, 1 ml) from Waters (Milford, MA, USA) were used. The sorbent of these cartridges is a macroporous polymer made from two monomers, the lipophilic divinylbenzene and the hydrophilic *N*-vinylpyrrolidone.

The cartridges were activated with 1 ml of methanol and conditioned with 1 ml of water, then loaded with 500 μl of plasma diluted with 500 μl of water and spiked with 20 μl of triprolidine (I.S.) solution at the concentration of 100 ng ml^{-1}.

The cartridge was then washed twice with 1 ml of pH 10.3, 100 mM carbonate buffer/methanol (80/20, v/v) mixture and once with 1 ml of water, and the analyte was eluted with 1.5 ml of methanol. The eluate was then brought to dryness in a rotary evaporator and redissolved with 100 μl of mobile phase. The resulting solution was injected into the HPLC.

2.7. Method validation

The method validation assays were carried out according to the 'Crystal City' [32] guidelines. Calibration curves were set up on blank plasma, by adding known amounts of quetiapine standard solution to known volumes of blank plasma and subjecting the resulting mixture to the SPE procedure described above and to HPLC analysis. The calibration curve was constructed plotting the quetiapine/I.S. peak area ratio against the concentration of quetiapine added and applying the least-square method. The detection limit (LOD) and quantitation limit (LOQ) were determined as three and 10 times the baseline noise, respectively, following the United States Pharmacopeia [33] and 'Crystal City' [32] guidelines.

2.7.1. Absolute recovery

Known amounts of quetiapine standard solution and of I.S. were added to known amounts of blank plasma samples. The extraction yield (or absolute recovery) was determined by comparing the quetiapine/I.S. peak area ratios obtained following the outlined extraction procedure with those obtained by injecting standard solutions having the same theoretical concentration. This procedure was repeated for the three different concentrations of quetiapine added, namely 4, 100 and 400 ng ml^{-1} and 40 ng ml^{-1} of I.S.

2.7.2. Precision assays

Precision was judged by subjecting six separate blank plasma samples spiked with the same analyte concentrations as per 'Absolute Recovery' to the extraction procedure. The resulting solutions were then injected into the HPLC. A relative standard deviation (RSD) value was obtained repeating the assays six times in the same day for intraday precision (repeatability) and on 6 different days for interday precision (intermediate precision).

2.7.3. Accuracy

Known amounts of quetiapine and I.S. standard solutions were added to known amounts of plasma samples taken from patients. The method accuracy was evaluated by calculating the difference between the spiked sample peak area ratios and the original sample peak area ratios, then comparing these differences with the peak areas obtained by injecting standard solutions having the same concentration as the sample spiking. The concentrations added were 10 and 100 ng ml^{-1} of quetiapine and 40 ng ml^{-1} of I.S. The procedure was repeated three times to obtain SD values.

3. Results and discussion

3.1. HPLC conditions

The last paper on clozapine determination in human plasma [27] was the starting point for the development of this HPLC method for the determination of quetiapine. The method [27] used a Varian Microsorb MV C18 reversed phase column (150 × 4.6 mm i.d., 5 μm) and a mobile phase composed of acetonitrile–methanol—10.4 mM, pH 1.9 phosphate buffer (17.5:20:62.5, v/v/v), containing 0.25% (v/v) triethylamine. The clozapine analysis was carried out by means of HPLC with amperometric detection (oxidation potential: +800 mV), however this was not possible for quetiapine which is not electroactive, hence spectrophotometric detection was used.

In order to choose the detection wavelength of the HPLC–UV method, preliminary spectrophotometric studies were carried out on standard quetiapine solutions in acidic medium (phosphate buffer/methanol/acetonitrile mixture, pH* = 2.5). The spectrum of quetiapine (Fig. 2a) showed one absorbance peak with a maximum at 210 nm and two shoulders at $\lambda = 254$ and 290 nm. Since the detection at 210 nm would have been difficult because of the many potentially interfering compounds, we chose to carry out the analyses at $\lambda =$ 254 nm (this wavelength grants higher sensitivity than detection at 290 nm).

To optimize the chromatographic conditions, several assays were carried out by adding increasing percentages of water to the initial mobile phase: best results were found with a water percentage of 72%. Furthermore, the peak symmetry was enhanced by increasing the phosphate buffer concentration. Thus, the final composition of the mobile phase was: pH 1.9, 15.4 mM phosphate buffer (containing 11.5 mM triethylamine), methanol and acetonitrile in a 72:16:12 (v/v/v) ratio, flowing at 1 ml min^{-1}. Triprolidine (Fig. 1c) was chosen as the I.S.; as can be seen from its spectrum (Fig. 2b), this compound has good absorptivity at 254 nm.

Under these leading conditions, quetiapine is eluted as a neat peak at $t_R = 9.9$ min (Fig. 3), while the peak at $t_R = 5.8$ min corresponds to the I.S.

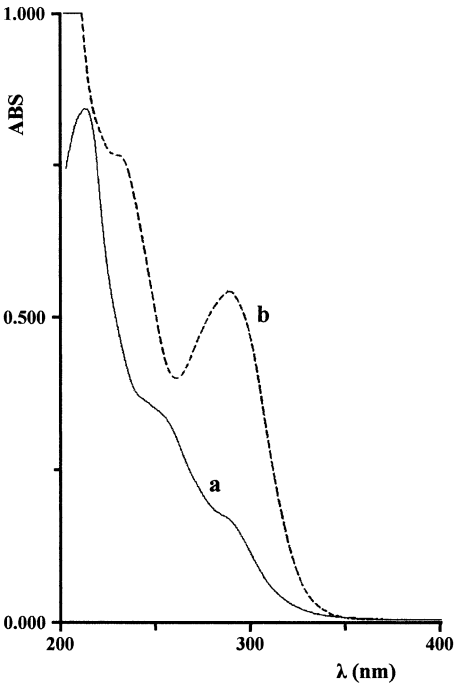

Fig. 2. Ultraviolet absorbance spectra of quetiapine (a) and triprolidine (b), each at a concentration of 20 μg ml^{-1}. Spectra recorded in acidic medium: phosphate buffer/methanol/acetonitrile mixture, pH* = 2.5.

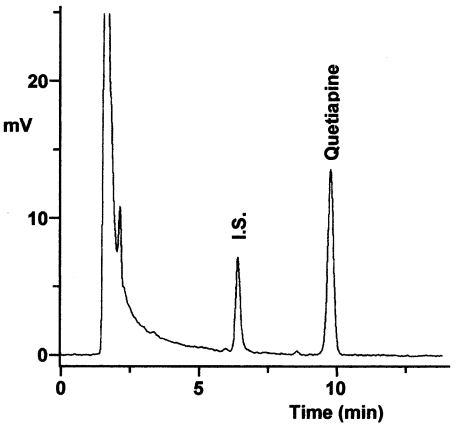

Fig. 3. Chromatogram of a standard solution containing 500 ng ml^{-1} of quetiapine and 200 ng ml^{-1} of I.S.

It can be noted that this choice of I.S. has the advantage of allowing rather short chromatographic times, shorter than those reported in earlier HPLC papers [9,22].

A calibration curve was set up in the 20–2000 ng ml^{-1} range, reporting quetiapine/I.S. peak area ratios versus analyte concentrations; good linearity was found ($y = 0.01102x - 0.0996$; $r^2 = 0.9996$).

Repeatability assays were carried out on quetiapine standard solutions, at concentrations corresponding to the lower and upper limit and the middle point of the calibration curve. Method precision was satisfactory: RSD% values of 3.4, 3.0 and 1.1 were obtained for quetiapine concentrations of 20, 500 and 2000 ng ml^{-1}, respectively.

3.2. Implementation of a new SPE procedure

In order to apply this method to the analysis of human plasma, a careful pretreatment of the biological sample has to be implemented. After several preliminary assays a simple and fast SPE method was developed. Oasis® HLB cartridges were used, loading 500 μl of plasma, washing with water and eluting with methanol. This procedure was sufficient to purify the sample from plasma interference and to extract the analyte (and the I.S.) almost completely. The eluate was then dried in a rotary evaporator and redissolved in a lower volume of mobile phase (100 μl): in this way, the concentration of quetiapine in the solution injected into the HPLC is five times that present in the original plasma sample, and this allows to reach the sensitivity needed for this assay, even using UV detection. However, with this SPE procedure the injection peak was broadened and the peaks of the analyte and the I.S. occured in a zone of marked baseline drift. For this reason, a new washing step was introduced into the initial SPE procedure: after loading the plasma sample, the cartridge was washed with a mixture of carbonate buffer and methanol. Preliminary assays showed that the highest percentage of methanol in the mixture which allowed to maintain a good extraction yield was 20%; thus, the washings were carried out by means of a pH 10.3, 100 mM carbonate buffer/methanol (80/20) mixture. The chromatogram of a blank plasma sample subjected to the modified SPE procedure is reported in Fig. 4a: as can be seen, no interfering peak is present.

The chromatogram of a blank plasma sample spiked with 100 ng ml^{-1} of quetiapine and 40 ng ml^{-1} of the I.S. is shown in Fig. 4b; the peaks are still neat and well separated, and have the same retention times as the peaks of standard solutions. Although some peaks from endogenous plasma components are present in the chromatogram, they do not interfere with the peaks of interest. A calibration curve was set up in the 4–400 ng ml^{-1} concentration range, and good linearity was obtained ($y = 0.01068x - 0.0750$; $r^2 = 0.9991$). The LOQ and LOD values of quetiapine in plasma were 4 and 1.5 ng ml^{-1}, respectively; both parameters were calculated according to United States Pharmacopeia XXV guidelines [33], that is, the analyte concentrations which give rise to signals ten and three times the baseline noise, respectively.

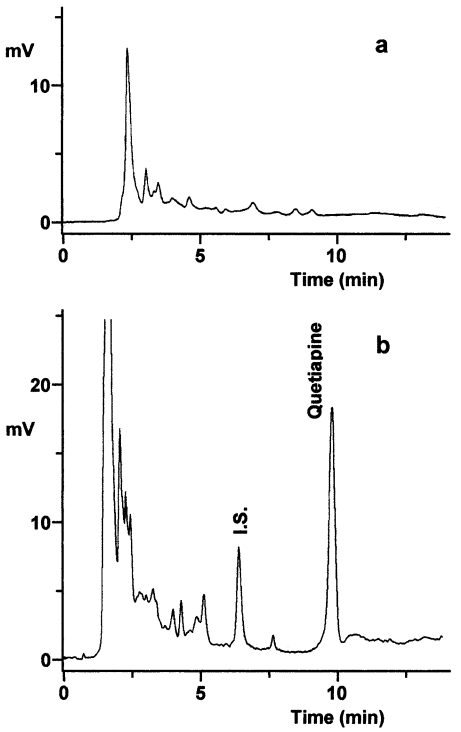

Fig. 4. Chromatogram of a blank plasma sample after the SPE procedure (a) and the same plasma sample spiked with 100 ng ml^{-1} of quetiapine and 40 ng ml^{-1} of I.S. (b).

This SPE procedure gave high extraction yields: Table 1 summarises the values of extraction yield obtained for quetiapine which are between 87.7

Table 1
Validation parameters

Quetiapine plasma concentration (ng ml^{-1})	Repeatability[a]		Intermediate precision[a]	
	Extraction yield (%)	RSD%	Extraction yield (%)	RSD%
10	87.7	3.9	88.5	4.4
100	89.6	3.1	90.2	4.0
400	91.6	1.9	93.0	2.5

[a] $n = 6$.

and 93.0%; the mean value of extraction yield for the I.S. is 88.3%.

Precision assays were carried out on blank plasma spiked with the analyte at concentrations corresponding to the lower limit, middle point and upper limit of the calibration curve; the respective data are reported in Table 1. The RSD% values are highly satisfactory: repeatability varied between 1.9 and 3.9%, while intermediate precision varied between 2.5 and 4.4%.

3.3. Selectivity studies

Several CNS drugs belonging to different therapeutic classes were tested for possible interference: antidepressants (amoxapine, dibenzepine, protriptiline, amitriptiline, maprotiline, imipramine, sertraline, fluoxetine, paroxetine), antipsychotics (clozapine, olanzapine, fluphenazine, clotiapine, risperidone), antiepileptics (phenobarbital, lamotrigine, oxcarbazepine, carbamazepine) and others. The results of these assays are reported in Table 2; as can be seen, none of the tested substances interfered with the analytical determination of quetiapine.

Table 2
Drugs tested for interference and their retention times

Compound	Therapeutic class	k'
Amitriptiline	Antidepressant	>11
Amoxapine	Antidepressant	8.45
Benserazide	DOPA decarboxilation inhibitor	n.d.
Carbamazepine	Antiepileptic	>11
Clotiapine	Antipsychotic	>11
Clozapine	Antipsychotic	2.90
Dibenzepine	Antidepressant	9.67
Fluoxetine	Antidepressant	>11
Fluphenazine	Antipsychotic	>11
Imipramine	Antidepressant	>11
Lamotrigine	Antiepileptic	1.99
Levodopa	Antiparkinson	1.62
Maprotiline	Antidepressant	>11
Melatonin	Hormone	6.32
Olanzapine	Antipsychotic	0.34
Oxcarbazepine	Antiepileptic	10.89
Paroxetine	Antidepressant	>11
Phenobarbital	Antiepileptic	4.49
Protriptiline	Antidepressant	>11
Quetiapine	*Antipsychotic*	*5.04*
Risperidone	Antipsychotic	7.60
Sertraline	Antidepressant	>11
Triprolidine	*Antihistaminic*	*2.54*

n.d. = not detected.

3.4. Application to patient plasma

The method was then applied to the analysis of some plasma samples from patients of the Psychiatric Clinic of the University of Bologna. The chromatogram of a plasma sample from a patient who took 300 mg per day of quetiapine is shown in Fig. 5; it is neat, the peaks of quetiapine and the I.S. are separated and well-defined, and no interfering peak is present. At least one other significant peak is present, at $t_R = 7.9$; this peak is observed in all analysed patient samples, and is presumably due to a quetiapine metabolite. This hypothesis could not be verified due to the lack of pure metabolites which could be used for the confirmation of identity. From the analysis of this sample, a quetiapine plasma concentration corresponding to 63 ng ml^{-1} was found. It should be noted that the sample was drawn from the patient 12 h after the last administration and immediately before the next administration, thus quetiapine was practically at its daily lowest

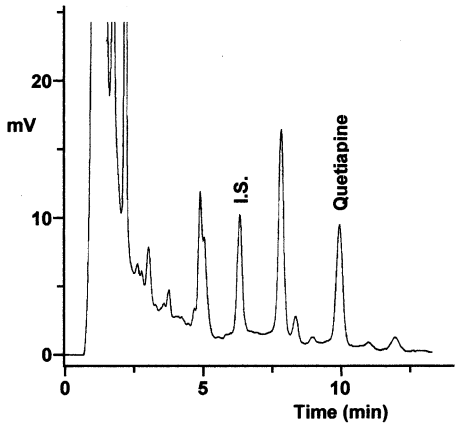

Fig. 5. Chromatogram of a plasma sample from a patient treated with 300 mg per day of quetiapine, after the SPE procedure.

concentration; nonetheless, the drug is still accurately quantifiable.

The accuracy of the method was estimated by means of recovery assays. Pre-analysed plasma samples of patients treated with quetiapine were spiked with quetiapine standard solutions at known concentrations, subjected to the SPE procedure, then analysed in HPLC. The percentage recovery values obtained are between 90.8% (SD $\pm$6.4) for an added concentration of 10 ng ml^{-1} and 95.2% (SD $\pm$5.1) for an added concentration of 100 ng ml^{-1}, hence the accuracy of the method is good.

4. Conclusion

The proposed method for the determination of quetiapine in human plasma based on the use of liquid chromatography with spectrophotometric detection resulted to be simple, accurate and precise. Moreover, the method is fast and feasible. In fact, the original SPE procedure developed for the pretreatment of plasma samples is less polluting and time-consuming than the liquid–liquid extraction procedures used by other authors [9,23]. The only other method which uses SPE is time-consuming and requires higher volumes of sample [22]. The extraction yield values of quetiapine from plasma samples are much higher than those previously reported by other authors [9] (88–93 vs. 39–47%), and precision was also better (mean RSD% = 3.3 vs. 11.9%). Our method shows satisfactory sensitivity having LOQ = 4 ng ml^{-1}, which is much better than the LOQ of 100 ng ml^{-1} reported for the GC method [23], better than the LOQ of 15 ng ml^{-1} of the first published HPLC method [22] and comparable to the LOQ of 2.5 ng ml^{-1} of the second HPLC method [9].

Furthermore, it has good selectivity; in fact, no interference was found upon examining 21 different CNS drugs.

In conclusion, the method is suitable for the analysis of quetiapine in human plasma, and it seems to be very promising for the TDM of patients undergoing chronic treatment with quetiapine.

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References

[1] J.A. Worrel, P.A. Marken, S.E. Beckman, V.L. Ruether, Am. J. Health-Syst. Ph. 57 (2000) 238–255.
[2] T.I. Prior, P.S. Chue, P. Tibbo, G.B. Baker, Eur. Neuropsychopharm. 9 (1999) 301–309.
[3] C.L. DeVane, C.B. Nemeroff, Clin. Pharmacokinet. 40 (2001) 509–522.
[4] C.F. Caley, S. Rosenbaum, Formulary 33, 105–106, 109–110, 112, 115–116, 119 (1998).
[5] N.S. Gunasekara, C.M. Spencer, CNS Drugs 9 (1998) 325–340.
[6] P. Meats, Int. J. Psych. Clin. Pract. 1 (1997) 231–239.
[7] J. Mullen, M.D. Jibson, D. Sweitzer, Clin. Ther. 23 (2000) 1839–1854.
[8] L.A. Arvanitis, B.G. Miller, Biol. Psychiat. 42 (1997) 233–246.

[9] P.C. Davis, J. Wong, O. Gefvert, J. Pharmaceut. Biomed. 20 (1999) 271–282.
[10] P.J. Weiden, J. Prac. Psych. Behav. Health 3 (1997) 368–374.
[11] S. Kasper, F. Muller-Spahn, Expert Opin. Pharmacother. 1 (2000) 783–801.
[12] J.G. Small, S.R. Steven, L.A. Arvantis, B.G. Miller, C.G.G. Link, Arch. Gen. Psychiat. 54 (1997) 549–557.
[13] M. Hasegawa, P.A. Cola, H.Y. Meltzer, Neuropsychopharmacology 11 (1994) 45–47.
[14] J.M. Goldstein, Drugs Today 35 (1999) 193–210.
[15] N. Mohr, B. Vythilingum, R.A. Emsley, D.J. Stein, Int. Clin. Psychopharm. 17 (2002) 37–40.
[16] P. Pollak, K. Zbuk, Clin. Pharmacol. Ther. 68 (2000) 92–97.
[17] D.E. Casey, J. Clin. Psychiat. 58 (1997) 55–62.
[18] J.A. Shaw, J.E. Lewis, S. Pascal, R.K. Sharma, R.A. Rodriguez, R. Guillen, M. Pupo-Guillen, J. Child Adol. Psychop. 11 (2001) 415–424.
[19] F. Hayden, J. Child Adol. Psychop. 11 (2001) 289–293.
[20] V. Dev, J. Raniwalla, Drug Safety 23 (2000) 295–307.
[21] M.A. Raggi, Curr. Med. Chem. 9 (2002) 1241–1253.
[22] R.H. Pullen, K.M. Palermo, M.A. Curtis, J. Chromatogr. 573 (1992) 49.
[23] D.T. Anderson, L.K. Friz, J. Anal. Toxicol. 24 (2000) 300–304.
[24] V. Pucci, R. Mandrioli, A. Ferranti, S. Furlanetto, M.A. Raggi, J. Pharmaceut. Biomed. in press.
[25] M.A. Raggi, F. Bugamelli, R. Mandrioli, D. De Ronchi, V. Volterra, Chromatographia 47 (1998) 8–12.
[26] M.A. Raggi, F. Bugamelli, R. Mandrioli, D. De Ronchi, V. Volterra, Chromatographia 49 (1999) 75–80.
[27] M.A. Raggi, F. Bugamelli, C. Sabbioni, D. De Ronchi, S. Pinzauti, V. Volterra, Chromatographia 51 (2000) 147–153.
[28] M.A. Raggi, G. Casamenti, R. Mandrioli, S. Fanali, D. De Ronchi, V. Volterra, Chromatographia 51 (2000) 562–566.
[29] M.A. Raggi, G. Casamenti, R. Mandrioli, V. Volterra, J. Chromatogr. B 750 (2001) 137–146.
[30] M.A. Raggi, R. Mandrioli, C. Sabbioni, N. Ghedini, S. Fanali, V. Volterra, Chromatographia 54 (2001) 203–207.
[31] M.A. Raggi, S. Fanali, R. Mandrioli, F. Bugamelli, V. Volterra, HPLC analysis of the novel antipsychotic drug quetiapine in human plasma, 2nd International Symposium on Separations in the Biosciences, Prague, September 17–20, 2001 (Abstract book p. 126).
[32] H.M. Hill, Chromatographia 52 (2000) 65–72.
[33] United States Pharmacopeia, 24th Edition, United States Pharmacopeial Convention, Rockville (MD) (2000) pp. 2150–2151.