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Simplified ultraviolet liquid chromatographic method for determination of sertindole, dehydrosertindole and norsertindole, in human plasma

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Abstract

An ultra-violet high-performance liquid chromatographic method was developed for the determination of sertindole, an atypical antipsychotic drug and its main metabolites dehydrosertindole and norsertindole, in human plasma. With a small sample volume, after a single-step liquid–liquid extraction, the compounds were separated on a reversed-phase XTerra® RP_{18} column, eluted with 45% of acetonitrile and 55% of ammonium acetate buffer (0.05 M, adjusted pH 8) and detected at 256 nm within 11 min. This method shows a good linearity for plasma concentration between 5–100 ng/ml and 100–1000 ng/ml, a good precision (inter and intra day CV < 11%) and a good inter-assay accuracy (bias < 11%). The limit of quantification concentration was 5 ng/ml. The absolute recovery of sertindole was higher than 99%. This rapid and sensitive method could be used for therapeutic drug monitoring as well as for overdose management.

Keywords: Sertindole; Human plasma; Liquid–liquid extraction; Drug monitoring; Overdose

1. Introduction

Sertindole,1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolodinone (Fig. 1), is an atypical antipsychotic drug introduced on the market in 1996. Sertindole is a serotonin 5-HT_{2A} and 5-HT_{2C}, dopamine D_2 and α_1-adrenergic antagonist with selective effects on mesolimbic but not on nigrostriatal dopaminergic neurons [1–3] Because of this neurologic selectivity, sertindole is effective in the treatment of both positive [4] and negative [5,6] symptoms in schizophrenia, with fewer extrapyramidal effects than classical neuroleptics [4,7,8]. Based on these findings, sertindole is regarded as one of the atypical antipsychotic drugs such as risperidone, clozapine, olanzapine and ziprasidone. This drug is therefore attractive to clinicians because of its efficacy on the symptoms of schizophrenia and its fewer extrapyramidal side effects.

During preclinical [9,10] and clinical [11,12] trials, sertindole has shown a capacity to prolong the QT interval on electrocardiogram without apparently increase the risk of cardiac death. In 1998, sertindole was suspended from the market because of a drug alert regarding sertindole from the UK MCA's database of spontaneous reports: reports of sudden deaths were ten times higher for sertindole than for the other atypical antipsychotics [13]. After further preclinical [14–16], clinical and epidemiological [13] studies, sertindole was re-introduced in 2001 with some precautions and additional counter-indications.

In man, sertindole is metabolized in two compounds, dehydrosertindole and norsertindole (Fig. 1), by CYP 2D6 and CYP 3A4, respectively [17,18]. Due to this metabolic pathway, inter and intra-individual plasma concentration

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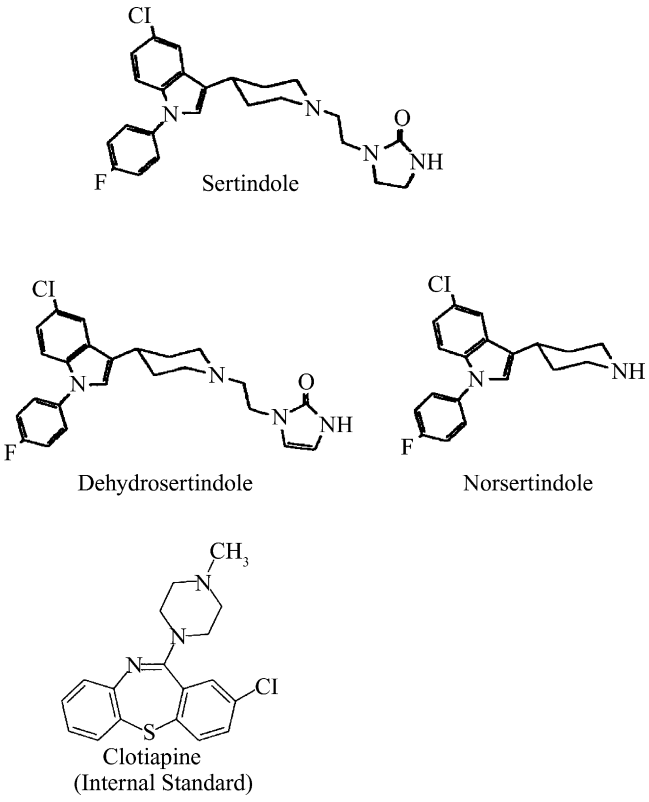

Fig. 1. Chemical structure of sertindole, its main metabolites and internal standard.

variations may occur for sertindole. Impairment of hepatic function would be expected to be followed by lower clearance. Genetic polymorphism of CYP 2D6 participates to the interindividual pharmacokinetic variation: there is a 33–50% sertindole clearance decrease in poor 2D6 metabolizers. During population pharmacokinetic studies, potent CYP 2D6 inhibitors such as fluoxetine or paroxetine, possibly coadministered with sertindole treatment, increase sertindole plasma concentration two- to three-fold and decrease its clearance by half [19]. Potent CYP 3A4 inhibitors such as macrolides increase sertindole plasma concentration less than 25%. On the other hand, enzyme inducers such as carbamazepine or phenytoïne can increase the clearance of sertindole, so that sertindole concentration would decrease by a factor of 2–3 and consequently efficacy would be less [19].

All those interactions show the utility of sertindole determination for dose adaptation, in case of coadministration. Moreover, therapeutic drug monitoring of sertindole might be useful because of the concentration-dependent QT interval prolongation shown in vitro [9,20], the relationship between QT interval prolongation and sertindole doses [6] or sertindole plasma concentrations [11]. In overdose cases, due to the long half-life of sertindole in man (3–5 day), and its QT prolongation capacity, it would be also useful to follow the sertindole concentrations.

Actually, two methods for the determination of sertindole and its metabolites have been published. A fluorimetric high-performance liquid chromatography (HPLC) procedure was developed for sertindole in a lower concentration range (0.025–4 ng/ml), than therapeutic plasma concentrations [21]. An LC–MS–MS procedure was performed for the assay of sertindole and its metabolites in human, rat, dog and mouse plasma during pharmacokinetic preclinical and clinical trial [22]. However, such expensive equipment is not available only in all laboratories.

The purpose of this study was to develop a simple, rapid, accurate, sensitive and specific method for the determination of sertindole and its main metabolites in plasma, which can be currently used for therapeutic monitoring or poison management.

2. Experimental

2.1. Chemicals

Sertindole (Lu 23–174), dehydrosertindole (Lu 28–092) and norsertindole (Lu 25-073) were generously donated by Lundbeck (Copenhagen, Denmark). Clotiapine (Fig. 1), the internal standard (IS) was purchased from Novartis (Rueil-Malmaison, France). The purity of these compounds was greater than 99%. Sodium hydroxide, hydrochloric acid and ammonium acetate were from Merck (Darmstadt, Germany). Hexane, isoamylic alcohol, acetonitrile were from JT Baker (Deventer, Holland) and methanol from Carlo Erba (Val de Reuil, France). All reagents were of HPLC-grade quality. Water was deionized and purified using a Milli-Q system (Millipore, Bedford, MA, USA). Heparinized healthy human volunteers plasma was purchased from Etablissement de Transfusion Sanguine d'Aquitaine (ETSA, Bordeaux, France).

2.2. Standard solutions

Stock solutions of sertindole, dehydrosertindole and norsertindole, for generating calibration curves, were prepared in methanol to yield concentrations of 1 mg/ml and stored at −20 °C. They were stable for at least 4 months. The 1 mg/ml IS stock solution in methanol was diluted daily in deionized water to yield a 400 ng/ml working solution.

The calibration standards were made in drug free plasma to yield concentrations of 5, 10, 20, 50, 80 and 100 ng/ml. For the preparation of quality controls used for the validation of the assay, independent stock solutions containing the compounds were prepared and further diluted in blank plasma to achieve concentrations of 5, 30, 70 and 90 ng/ml.

For assay in overdose, this method was also validated in a higher range of concentration, up to ten times the therapeutic concentrations: plasma standard samples were at 100, 200, 500, 800, 1000 ng/ml and quality control samples at 300, 600 and 900 ng/ml.

2.3. Equipment

The high-performance liquid chromatography system consisted of a constant flow pump (515, Waters Corp.,

Milford, MA, USA), an autoinjector (717 plus autoinjector, Waters Corp.), a model UV 1000 ultraviolet detector (Spectraseries) and a recording-integrator (Datajet, Thermoquest, San José, CA, USA).

The chromatographic analysis was performed at +25 °C. The mobile phase consisted of a binary mixture of acetonitrile and ammonium acetate buffer (0.05 M, adjusted pH 8 with ammonia) (45:55, v/v). Before use, the mobile phase was filtered through a 0.2 μm nylon membrane. The mobile phase was delivered at a flow rate of 1.5 ml/min. The compounds were isocratically eluted on a reversed-phase XTerra® RP_{18} column (150 mm × 4.6 mm, 5 μm, Waters) and then detected at 256 nm within 11 min.

2.4. Sample preparation

To 500 μl of plasma, 100 μl of the internal standard working solution (400 ng/ml), 2 ml of NaOH 2N and 8 ml of the extracting solvent hexane-isoamylic alcohol (99/1, v/v) were added. The mixture was shaken for 20 min, centrifuged at 3000 × *g* for 10 min. The organic phase was transferred to another tube and the aqueous layer was discarded. Two hundred microliters of HCL 0.05N was added to the organic phase. The mixture was shaken for 20 min and centrifuged at 3000 × *g* for 10 min. One hundred and fifty microliters of the aqueous phase was transferred to a micro vial for autosampler and 80 μl were injected by the auto-sampling injector.

2.5. Assay validation procedures

2.5.1. Absolute recovery

The absolute recovery was calculated by comparing the peak height after injection of the drugs dissolved in HCL 0.05N with the peak height after extraction of the same quantity of the compounds from the plasma (5, 30, 70, 90, 300, 600, 900 ng/ml, $n = 4$).

2.5.2. Linearity

The calibration curves were built by plotting the compound to internal standard peak height ratios versus the corresponding standard sample concentrations of the compound in ng/ml. Then, concentrations of sertindole, dehydrosertindole and norsertindole for unknown samples and quality control samples were obtained by using linear regression of the calibration curves.

2.5.3. Precision

The precision of the developed method was determined by analysis of eight quality control samples containing 5, 30, 50, 70, 90, 300, 600, and 900 ng/ml of each drug. Each of the quality control samples was replicates ($n = 6$) and analysed on 4 consecutive days. Subsequently, the mean of each set of the concentrations and the percent deviation of the quality control samples were calculated. One-way analysis of variance (ANOVA), with the day as variable of classification, was used to calculate the inter- and intra-assay variation.

The following formulas were used in order to calculate the inter-assay precision and intra-day precision, respectively:

$$\frac{[(\text{day mean square} - \text{error mean square})/n]^{1/2}}{\text{grand mean}} \times 100\%$$

$$\frac{(\text{error mean square})^{1/2}}{\text{grand mean}} \times 100\%$$

The day mean square, the error mean square and grand mean square are expressions originating from ANOVA. n is the number of replicates within each day (six) for each concentration. If the error mean square is higher than the day mean square the inter assay precision is regarded as zero. This signifies that no significant variation is observed as a result of performing the assay in different runs.

2.5.4. Accuracy

The intra- and inter-assay accuracies were expressed as percent bias calculated according to the following equation:

$$\text{bias (\%)} = \frac{\text{concentration}_{\text{measured}} - \text{concentration}_{\text{theoretical}}}{\text{concentration}_{\text{theoretical}}} \times 100$$

3. Results and discussion

This analytical method was developed for assaying both sertindole and its main metabolites in therapeutic concentrations range and overdose concentrations range.

A single-step liquid–liquid extraction procedure was performed for this purpose. This method is rapid, simple, selective and efficient, requiring about 1 h for an analyst to extract about 15 samples. It is also adapted to tissue homogenate samples [23] and avoids purchasing C_8 solid-phase extraction cartridges compared with solid–liquid extraction method [21].

3.1. Chromatography

Under the chromatographic conditions, sertindole, dehydrosertindole and norsertindole were sufficiently resolved from endogenous plasma compounds with no significant chromatographic interferent peaks (Fig. 2). Representative chromatograms of a blank plasma and plasma spiked with 10 and 80 ng/ml of sertindole, dehydrosertindole and norsertindole are presented in Fig. 2. The four compounds are chromatographed within 11 min.

3.2. Linearity

We focused our range of concentration on usual therapeutic man plasma concentrations averaging about 50–100 ng/ml

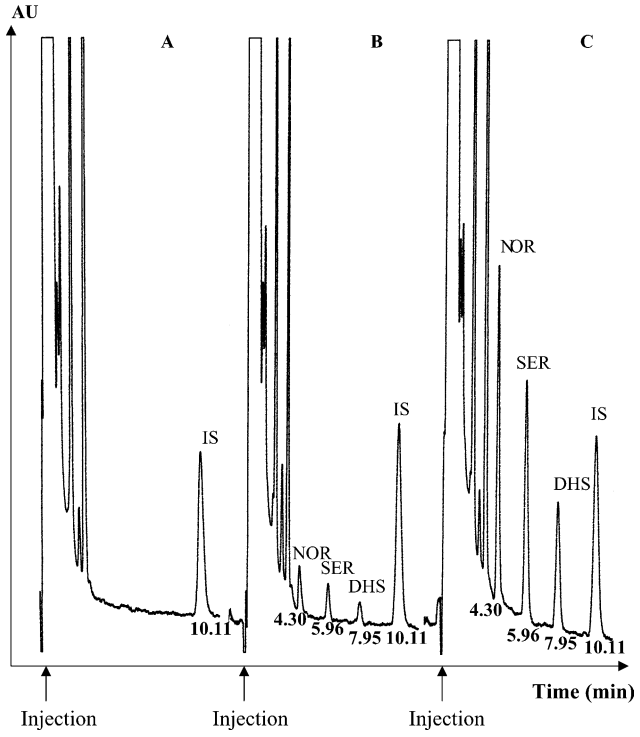

Fig. 2. Representative chromatograms of a blank plasma (A) and plasma spiked with 10 ng/ml (B), and 80 ng/ml (C) of sertindole (SER), dehydrosertindole (DHS) and norsertindole (NOR). IS: internal standard.

for sertindole, 37–70 ng/ml for dehydrosertindole and 15–40 ng/ml for norsertindoles: those concentrations were reached during chronic treatment with 12–24 mg dose of sertindole per day [24]. We also validated this method with a higher range of concentration between one to ten times the usual plasma concentration (100–1000 ng/ml) for detecting drug interaction and for sertindole assay in overdose.

For the validation of this method, all standard sample concentrations assayed over four days are pooled to build a calibration curve with a linear regression. The method revealed good linearity for the two ranges of concentrations with a correlation coefficient of 0.9958 for sertindole ($y = 0.0236x + 0.0177$), 0.9957 for dehydrosertindole ($y = 0.0161x + 0.0042$) and 0.9921 for norsertindole ($y = 0.0247x + 0.0662$), for the low range of concentration. For 100–1000 ng/ml concentration range, the correlation coefficients were 0.9979 ($y = 0.003x - 0.014$) for sertindole, 0.9979 for dehydrosertindole ($y = 0.002x - 0.01$), 0.9954 for norsertindole ($y = 0.004x - 0.092$).

3.3. Precision and accuracy

The method is accurate and precise for the two concentration ranges. Results obtained for precision and accuracy are listed in Tables 1 and 2. A good accuracy was achieved with a bias less than 11%, for inter-assay accuracies. For

Table 1
Data of the determination of sertindole and its metabolites in spiked plasma

	Day 1		Day 2		Day 3		Day 4	
	Mean ± S.D. ($n = 6$)	Bias (%)	Mean ± S.D. ($n = 6$)	Bias (%)	Mean ± S.D. ($n = 6$)	Bias (%)	Mean ± S.D. ($n = 6$)	Bias (%)
Sertindole (ng/ml)								
5	4 ± 0.2	−6.0	5 ± 0.3	+6.6	5 ± 0.6	−3.6	–	–
30	31 ± 2.6	+4.0	31 ± 1.1	+2.7	30 ± 1.4	+1.3	31 ± 1.6	+3.7
50	53 ± 4.3	+6.0	53 ± 3.0	+5.6	49 ± 1.3	−1.1	54 ± 2.4	+7.4
70	66 ± 3.9	−5.8	70 ± 5.4	−0.7	72 ± 2.3	+2.8	74 ± 1.5	+6.2
90	88 ± 5.5	−1.9	93 ± 4.9	+3.2	–	–	96 ± 2.1	+6.1
300	313 ± 7.7	+4.3	262 ± 8.0	−12.8	291 ± 10.1	−2.8	313 ± 12.2	+4.4
600	650 ± 14.8	+8.4	542 ± 42.4	−9.6	565 ± 63.6	−5.8	614 ± 76.0	+2.3
900	994 ± 22.7	+10.4	983 ± 31.8	+9.3	832 ± 14.6	−7.5	864 ± 125.3	−4.0
Dehydrosertindole (ng/ml)								
5	5 ± 0.5	+2.0	6 ± 0.4	+12.0	4.8 ± 0.7	−4.0	–	–
30	33 ± 1.9	+8.7	31 ± 1.9	+3.7	31 ± 1.2	+2.4	30 ± 1.6	−0.7
50	49 ± 3.5	−2.4	53 ± 1.9	+6.6	55 ± 1.7	+10.0	52 ± 2.1	+4.6
70	64 ± 3.9	−9.0	70 ± 4.3	−0.4	77 ± 1.1	+10.4	73 ± 2.1	+4.0
90	82 ± 7.4	−8.5	98 ± 7.1	+9.0	–	–	92 ± 1.9	+2.5
300	329 ± 10.6	+9.7	333 ± 36.1	+11.1	329 ± 31.8	+9.8	336 ± 28.3	+12.0
600	662 ± 20.3	+10.3	663 ± 68.9	+10.5	638 ± 73.2	+6.4	634 ± 81.7	+5.7
900	997 ± 35.4	+10.7	983 ± 123.1	+9.2	972 ± 89.8	+9.2	960 ± 95.4	+6.7
Norsertindole (ng/ml)								
5	5 ± 0.1	−2.0	5 ± 0.2	+4.0	5 ± 0.6	−2.0	–	–
30	31 ± 2.1	+3.3	29 ± 2.9	−2.0	30 ± 3.3	+0.7	29 ± 1.7	−3.0
50	51 ± 3.7	+2.2	50 ± 4.9	+0.6	53 ± 5.7	+5.2	48 ± 0.8	−4.8
70	78 ± 5.3	+10.9	63 ± 5.6	−9.4	72 ± 1.9	+2.4	68 ± 1.6	−2.1
90	97 ± 12.0	+7.8	92 ± 5.9	+2.1	–	–	86 ± 2.1	−4.2
300	276 ± 6.7	−7.9	266 ± 29.0	−11.1	270 ± 28.3	−10	265 ± 24.0	−11.7
600	567 ± 31.2	−5.5	578 ± 19.3	−3.3	553 ± 44.5	−7.7	525 ± 21.2	−12.5
900	831 ± 31.2	−7.6	807 ± 68.3	−10.3	811 ± 43.8	−9.9	815 ± 45.2	−9.4

Table 2
Precision and accuracy of the determination of sertindole and its metabolites in spiked plasma (data obtained by ANOVA)

Concentration (ng/ml)	Intra-assay precision (CV, %)	Inter-assay precision (CV, %)	Bias (%)
Sertindole			
5	8.2	3.9	−0.6
30	5.6	3.0	+2.9
50	8.3	2.3	+4.5
70	5.4	4.5	−2.5
90	4.7	3.2	+2.8
300	3.3	7.9	−1.7
600	9.2	5.0	−1.2
900	7.2	7.4	+2.0
Dehydrosertindole			
5	10.7	4.1	+3.4
30	5.4	2.6	+3.1
50	4.5	4.6	+4.8
70	4.8	6.9	−0.1
90	6.8	11.4	+3.1
300	8.5	2.1	+10.9
600	10.1	1.5	+8.2
900	9.4	1.8	+8.7
Norsertindole			
5	7.4	1.6	+0.6
30	8.7	0.7	−0.3
50	8.3	2.3	+0.8
70	6.7	8.0	−0.8
90	8.2	4.6	+1.5
300	8.8	1.5	−10.3
600	5.5	1.4	−7.4
900	6.0	1.9	−9.3

the two concentration ranges, a good intra- and inter-assay precision with a coefficient of variation (CV) less than 11% was achieved for sertindole and its metabolites. The limit of quantification (LOQ) was 5 ng/ml for the three compounds with an intra-assay and inter-assay precision with a CV less than 20%. Using a peak-to-noise ratio of 3 as a criterion, the estimated lower limit of detection was 3 ng/ml for the three compounds.

3.4. Absolute recovery

The absolute recoveries of each drug are presented in Table 3. The mean recoveries of sertindole, dehydrosertindole and norsertindole were 103% ± 2.7, 78% ± 2.2 and 88% ± 1.5 (mean ± S.D., $n = 16$), respectively. Internal standard recovery was 74% ± 3.25. For the higher range of concentrations, recoveries were, respectively, 107% ± 4.8 for sertindole, 107% ± 5.1 for dehydrosertindole and 102% ± 5.6 for norsertindole.

3.5. Stability

The stability of sertindole, dehydrosertindole and norsertindole in plasma was evaluated with three quality controls (50, 70, 90 ng/ml; $n = 4$), under different conditions: after 24 h on light or dark conditions at room temperature, after 72 h at +4 °C, after two repeated freeze–thaw cycles, and after two months at −20 °C storage.

Table 3
Absolute recovery for each concentration for sertindole and its metabolite

Concentration (ng/ml)	Absolute recovery (%) (mean ± S.D., $n = 4$)
Sertindole	
5	99 ± 7.8
30	103 ± 1.3
70	105 ± 5.2
90	104 ± 4.7
300	108 ± 6.9
600	105 ± 1.7
900	107 ± 5.1
Dehydrosertindole	
5	77 ± 0.5
30	77 ± 2.1
70	79 ± 4.5
90	79 ± 5.3
300	103 ± 0.8
600	106 ± 3.9
900	112 ± 5.1
Norsertindole	
5	86 ± 1.0
30	90 ± 1.8
70	89 ± 0.8
90	88 ± 4.1
300	95 ± 0.8
600	107 ± 3.6
900	104 ± 1.0

No degradation of sertindole or its metabolites was noted in frozen plasma over a period of two months, at −20 °C. Storage for 72 h at +4 °C or for 24 h at room temperature under either light or dark conditions produced no significant decrease of the three compounds, with relative standard derivation (R.S.D.) and bias values below than 10%. In addition, the three compounds also appeared to be stable after two repeated freeze–thaw cycles (R.S.D. and bias below than 10%).

3.6. Specificity

The drugs possibly associated with sertindole in schizophrenic patient were injected into the HPLC system at 1 μg/ml, directly diluted in acid phase and/or after plasma extraction, to assess possible chromatographic interference peak with sertindole, norsertindole, dehydrosertindole and clotiapine.

No interference was found from the most commonly used psychotropic drugs such as benzodiazepine (diazepam, clonazepam), antidepressor (fluoxetine, paroxetine) susceptible of being associated with sertindole in schizophrenic patients (Table 4).

3.7. Clinical cases

Serum sample of four patients treated chronically with 12–20 mg of sertindole per day were analyzed with this

Table 4
List of retention times (t_R) of tested interferences and sertindole, dehydrosertindole, norsertindole and clotiapine

Drugs	t_R (min)	Drugs	t_R (min)
Amisulpride	1.37	Desmethylclobazam	2.90
Acetylsalicylic acid	1.37	Fluoxetine	3.15
Furosemide	1.37	Imipramine	3.15
Loprazolam	1.37	Methadone	3.22
Metoclopramide	1.40	Dosulepine	3.40
Acebutolol	1.43	Haloperidol	3.55
Paracetamol	1.43	Clorazepate	3.63
Tiapride	1.43	Flunitrazepam	3.67
Midazolam	1.45	Nordiazepam	3.67
Ketoprofen	1.48	Clomipramine	3.80
Bromazepam	1.52	Norsertindole	4.30
9 OHrisperidone	1.52	Diazepam	4.75
Alprazolam	1.55	Amitryptiline	4.93
Mycophenolate	1.60	Clozapine	5.22
Lamotrigine	1.65	Zuclopentixol	5.23
Triazolam	1.68	Cyamemazine	5.32
Risperidone	1.77	Sertindole	5.96
7 Aminoflunitrazepam	1.82	Tetrazepam	6.55
Didemethylcitalopram	1.82	Loxapine	6.75
Oxcarbazepine	1.93	Mianserine	6.83
Tianeptine	2.03	Flupentixol	6.87
Olanzapine	2.08	Dehydrosertindole	7.85
Citalopram	2.15	Prazepam	8.95
Mirtazapine	2.25	Clotiapine (IS)	10.11
Atenolol	2.27	Pimozide	10.90
Carbamazepine	2.30	Amiodarone	n.d.
Fluvoxamine	2.45	Clobazam	n.d.
Desipramine	2.50	Clonazepam	n.d.
Chlordiazepoxide	2.63	Demethylvenlafaxine	n.d.
Doxepine	2.65	Ibuprofen	n.d.
Oxazepam	2.65	Loflazepate	n.d.
Zolpidem	2.67	Maprotiline	n.d.
Nortryptiline	2.80	Meprobamate	n.d.
Paroxetine	2.80	Minalcipram	n.d.
Cocaïne	2.82	Penfluridol	n.d.
Codeine	2.82	Norfluoxetine	n.d.
Codethylline	2.82		
Primidone	2.82		
Morphine	2.82		
Pholcodine	2.82		
Venlafaxine	2.82		
Zopiclone	2.82		
Lorazepam	2.87		

n.d.: no detectable peak from 0 to 20 min after extraction of plasma containing drug in usual therapeutic concentration.

method. Fig. 3 shows chromatograms obtained by extraction of plasma of two patients both treated by 20 mg of sertindole per day. The patient no. 2 was also treated with diazepam. Concentrations reached were between 30 and 98 ng/ml for sertindole, between 33 and 64 ng/ml for dehydrosertindole and between 24 and 61 ng/ml for norsertindole. Usual therapeutic man plasma concentrations average 50–100 ng/ml for sertindole, 37–70 ng/ml for dehydrosertindole and 15–40 ng/ml for norsertindole [24]. These assays show the validity of the 5–100 ng/ml range of concentrations, for therapeutic drug monitoring.

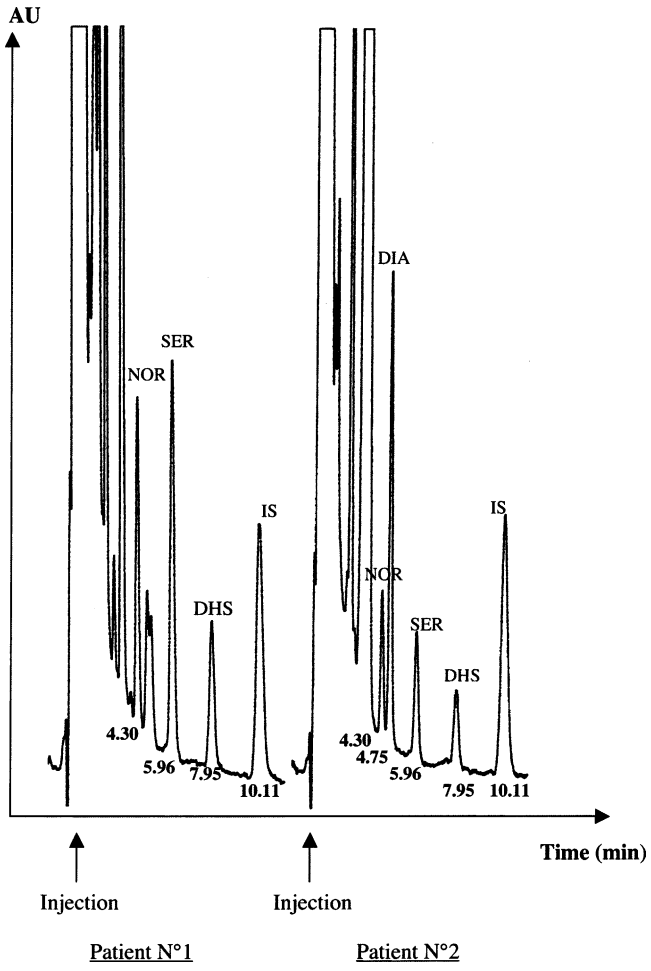

Fig. 3. Representative chromatograms of plasma from two patients chronically treated with sertindole. NOR for norsertindole, SER for sertindole, DHS for dehydrosertindole, IS for internal standard, DIA for diazepam.

4. Conclusion

In summary, this ultra-violet high-performance liquid chromatographic method is specific, sensitive, rapid and easy to perform. The liquid–liquid phase extraction allows high recovery, resulting in high sensitivity and excellent accuracy and precision. The limit of quantification, small sample volume and short chromatographic time of this assay are particularly adapted to routine assay. With the simultaneous determination of sertindole and its main metabolites in human plasma, this analytical procedure could be used for therapeutic drug monitoring and for overdose management.

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References

[1] C. Sanchez, J. Arnt, N. Dragsted, J. Hyttel, H. Lembol, E. Meier, J. Perregaard, T. Skarsfeldt, Drug Dev. Res. 22 (1991) 239.
[2] J. Arnt, T. Skarsfeldt, Neuropsychopharmacology 18 (1998) 63.
[3] J. Hyttel, J. Arnt, B. Costall, A. Domeney, N. Dragsted, H.L. Lembol, E. Meier, R.J. Naylor, G. Nowak, C. Sanchez, et al., Clin. Neuropharmacol. 15 (Suppl. 1 Pt A) (1992) 267A.
[4] P.T. Martin, J.A. Grebb, P. Schmitz, Schizophr. Res. 11 (1994) 107.
[5] D.G. Daniel, P. Wozniak, R.J. Mack, B.G. McCarthy, Psychopharmacol. Bull. 34 (1998) 61.
[6] D.L. Zimbroff, J.M. Kane, C.A. Tamminga, D.G. Daniel, R.J. Mack, P.J. Wozniak, T.B. Sebree, B.A. Wallin, K.B. Kashkin, Am. J. Psychiatry 154 (1997) 782.
[7] D.P. Van Kammen, J.P. McEvoy, S.D. Targum, D. Kardatzke, T.B. Sebree, Psychopharmacology (Berl.) 124 (1996) 168.
[8] S. Leucht, G. Pitschel-Walz, D. Abraham, W. Kissling, Schizophr. Res. 35 (1999) 51.
[9] M.D. Drici, W.X. Wang, X.K. Liu, R.L. Woosley, D.A. Flockhart, J. Clin. Psychopharmacol. 18 (1998) 477.
[10] D. Rampe, M.K. Murawsky, J. Grau, E.W. Lewis, J. Pharmacol. Exp. Ther. 286 (1998) 788.
[11] N. Moore, Internal document, Lundbeck SA (1999).
[12] N.A. Moore, Br. J Psychiatry Suppl. (1999) 5.
[13] N. Moore, G. Hall, M. Sturkenboom, R. Mann, R. Lagnaoui, B. Begaud, Pharmacoepidemiol. Drug Saf. 12 (2003) 271.
[14] S. Kongsamut, J. Kang, X.L. Chen, J. Roehr, D. Rampe, Eur. J. Pharmacol. 450 (2002) 37.
[15] L. Eckardt, G. Breithardt, W. Haverkamp, J. Pharmacol. Exp. Ther. 300 (2002) 64.
[16] M.B. Thomsen, P.G. Volders, M. Stengl, R.L. Spatjens, J.D. Beekman, U. Bischoff, M.A. Kall, K. Frederiksen, J. Matz, M.A. Vos, J. Pharmacol. Exp. Ther. 307 (2003) 776.
[17] L. Ereshefsky, J. Clin. Psychiatry 57 (Suppl. 11) (1996) 12.
[18] K. Sakamoto, Y. Nakamura, S. Aikoh, T. Baba, J. Perregaard, H. Pedersen, E.K. Moltzen, D.J. Mulford, T. Yamaguchi, Xenobiotica 25 (1995) 1327.
[19] EMEA, International Conference of Harmonisation, Safety-Topics S7B, www.emea.org, 2002.
[20] R.L. Woosley, Internal document, Lundbeck SA (1999).
[21] T.B. Tzeng, G. Stamm, S.Y. Chu, J. Chromatogr. B Biomed. Appl. 661 (1994) 299.
[22] S. Menacherry, G. Stamm, S. Chu, J. Liq. Chromatogr. Relat. Technol. 20 (1997) 2241.
[23] M. Canal-Raffin, K. Titier, E. Déridet, B. Martinez, A. Abouelfath, S. Gromb, M. Molimard, N. Moore, Biopharn. Drug Dispos., in press.
[24] Abbott-Laboratories, Drug Metabolism Report No. 56 (1995).