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LC determination of oxcarbazepine and its active metabolite in human serum

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Abstract

Twenty-five percent of epileptic patients present refractory seizures to current frontline antiepileptic drugs, needing new treatments and leading to the introduction of several new AEDs, among which is oxcarbazepine (Trileptal®). This 10-ketoanalogue of carbamazepine seems to be a weaker inducer of cytochrome P450 3A4. However, pharmacokinetic interactions with clinical significance have already been reported, before the marketing of Trileptal® in France. The aim of this study was to develop and validate a HPLC method allowing simultaneous dosage of oxcarbazepine, 10-hydroxycarbamazepine, epoxycarbamazepine, carbamazepine, phenobarbital and phenytoïn. After plasma defecation by acetonitrile, dosage was obtained by analysis of the supernatants on a C_{18} reversed-phase column coupled with UV detection (240 nm). The statistical validation was performed according to the recommendations of a European technical commission. This method seems to provide a quite good selectivity from the psychotropic therapeutics, which is commonly coprescribed with AEDs. Linearity was established for the whole concentration range, whatever the compound. Quantization limits of oxcarbazepine, 10-hydroxycarbamazepine, epoxycarbamazepine, carbamazepine, phenobarbital and phenytoïn are 0.58, 3.5, 2.35, 0.66, 1.02 and 3.13 μg/ml, respectively, and absolute recoveries are 105.15, 84.76, 94.45, 96.52, 98.62 and 95.08%, respectively.

Keywords: Antiepileptic drugs; HPLC; Simultaneous dosage; Oxcarbazepine; Carbamazepine; Phenytoïne; Phenobarbitone; Metabolite; UV detection

1. Introduction

About 10 years ago, epileptic seizures were still managed by current frontline antiepileptic drugs (AEDs), such as carbamazepine (CBZ), phenytoïn (PHT), valproic acid, ethosuximide, phenobarbitone (PBB) and benzodiazepines. However, 25% of patients presented refractory seizures to these therapies, needing new treatments that have led to the introduction of several new AEDs.

The anticonvulsivant efficacy of these drugs does not seem to increase significantly in compari-

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son with traditional AEDs [1,2]. Nevertheless, comedications of traditional AEDs with these drugs allow combining at least two different anticonvulsivant mechanisms of action and to improve therapeutic response. Moreover, the main advantages of these newly developed AEDs are less adverse events and pharmacokinetic interactions with other therapeutics [3].

Among the newly marketed drugs, oxcarbazepine (OXC), a 10-ketoanalogue of carbamazepine has been registered for use as add-on or first-line treatments in patients with generalized tonic–clonic seizures (not yet in France) and partial seizures with or without secondary generalization [4].

According to Novartis Laboratories, OXC may not be an active inducer of cytochrome P450 3A4 as carbamazepine. However, pharmacokinetic interactions with clinical significance have already been reported, when OXC was associated with felodipine, lamotrigine, valproic acid or phenytoin, suggesting that a larger use of OXC could lead to many other interactions [5–10].

In order to be able to detect these interactions, we developed a HPLC method with UV detection for dosage of OXC and its active metabolite, the 10-hydroxy carbamazepine (10OH-CBZ) in human serum. Thanks to this method, the simultaneous dosage of OXC, 10OH-CBZ, epoxycarbamazepine, carbamazepine, phenobarbital and phenytoïn could be performed. The simultaneous evaluation of these AEDs serum levels is very important to realize drug monitoring during switch between current AEDs and OXC. The difficulty to develop a simultaneous AEDs serum level measure is due to the similitude of physico-chemical properties and structures (Fig. 1). Simultaneous determination of phenobarbital, carbamazepine and phenytoïn was reported earlier. However, the simultaneous determination of oxcarbazepine and its active metabolite was not usually described. Wad [13] was the only one to propose a method for the simultaneous determination of oxcarbazepine, 10-hydroxy carbamazepine and traditional AEDs, but it required a HPLC method by elution gradient. Then, we choose to develop an isocratic elution method employing usual equipments in a clinical pharmacokinetic department.

2. Materials and methods

2.1. Drugs and chemicals

OXC, 10-hydrocarbamazepine (10OH-CBZ), CBZ and epoxycarbamazepine (epoxy-CBZ) were all gifts from Novartis laboratories (Rueil Malmaison, France). PHT, PBB and oxazepam were obtained from Sigma (St Quentin Fallavier, France). Drugs used to check the method selectivity were kindly provided by Janssen Cilag, Novartis, Organon and Pfizer laboratories.

Acetonitrile was purchased from Flandres Chimie (Villeneuve d'Ascq, France) and sodium acetate from Merck (Nogent/Marne, France). Solvents for mobile phase were of HPLC grade and others were of analytical reagent grade.

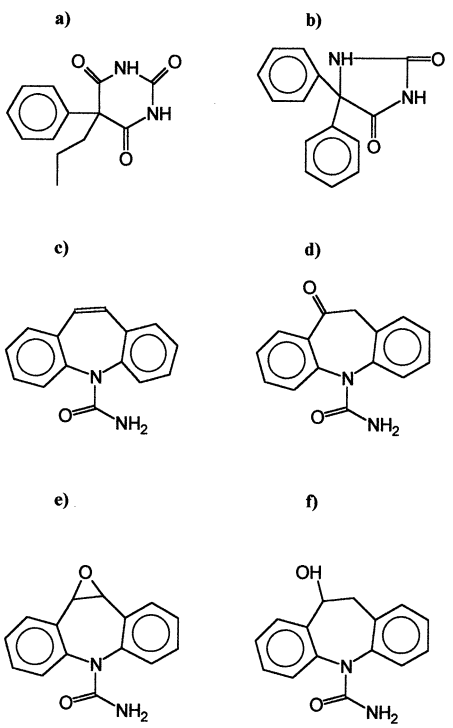

Fig. 1. AEDs' structure: a, PBB; b, PHT; c, CBZ; d, OXC; e, epoxy-CBZ; f, 10OH-CBZ.

2.2. Calibration solution

Three stock solutions (1 mg/ml) were prepared for each drug by dissolving OXC, 10OH-CBZ, epoxy-CBZ, CBZ, PBB, PHT or oxazepam (internal standard) in acetonitrile. Each was used to supply two calibration ranges with six different concentrations (36 samples).

Working solutions were prepared to obtain final concentrations from 0.5 to 150 μg/ml for PBB, 0.5 to 150 μg/ml for 10OH-CBZ, 0.5 to 100 μg/ml for OXC and CBZ and 2 to 100 μg/ml for epoxy-CBZ and PHT.

To fit the calibration curves according to European recommendations' group [11], 500 μl drug-free serum samples (Biotrol, France) was added to 50 μl of calibration dilutions and 100 μl of internal standard dilution (200 μg/ml), then made up to 1 ml with acetonitrile. Samples were vortexed for 1 min, then centrifuged twice for 10 min at 3000 rpm. Twenty microliters of supernatant was injected into the HPLC column by a Kontron 360 autosampler (Kontron, France).

In order to calculate the recovery of these drugs in serum, three levels of each drug were prepared, using an identical procedure in medium containing serum or acetonitrile alone.

2.3. Apparatus and accessories

The HPLC consisted of a Shimadzu LC10AT pump, a Shimadzu SPD10A variable wavelength detector set at 240 nm and a Shimadzu C-R5A model integrator recorder (Touzart and Matignon, Courtaboeuf, France).

Two reversed-phase columns were tested: the first was a C_8 Ultrabiosep (150 × 4.6 mm), particle size 5 μm (Hypersil) with guard-column (C_8 Ultrabiosep (10 × 4.6 mm), Hypersil); and the second was a C_{18} Ultrabiosep (150 × 4.6 mm), particle size 5 μm (Hypersil) with guard-column (C_{18} Ultrabiosep (10 × 4.6 mm), Hypersil).

In the initial conditions, the mobile phase was a mixture of sodium acetate buffer (7 mM, pH 5.4) and acetonitrile (68:32, v/v). Chromatography was carried out at room temperature with a flow-rate of 2 ml/min.

3. Results

3.1. Choice of assay conditions

The stock solutions used for calibration could be stored stably at −20 °C for up to 1 month. The working solutions prepared by diluting stock solutions with acetonitrile, and extract solutions were injected immediately into the chromatographic system. No stability study was realized on these solutions.

With an Ultrabiosep C_8 column and CH_3COONa (7 mM, pH 5.4)–acetonitrile (68:32) as the mobile phase, PBB and OXC were not separated. The retention time was reduced with a decrease of the mobile phase pH (8 to 2.2) but this did not lead to a better separation of the AEDs, PBB and OXC in particular. Changing the mobile phase composition to 40% acetonitrile did not bring about a best separation.

After this step, we tested a C18 Ultrabiosep column. This column with a more lipophilic stationary phase is able to retain OXC and PBB differently. Similar pH and mobile phase conditions to those with C8 column were tested. Using this C_{18} column and reducing acetonitrile concentration to 22% allowed separating the six compounds. The stabilization of the pH at 7 allowed separating epoxy-CBZ from PBB in order to avoid interferences in PBB quantization (Fig. 2). In these conditions the retention times were, 3.96 ± 0.021, 5.19 ± 0.076, 6.57 ± 0.025, 8.39 ± 0.020, $16{,}85 \pm 0.021$, 19.06 ± 0.063 and 26.11 ± 0.103 min for 10OH-CBZ, PBB, epoxy-CBZ, OXC, CBZ, PHT and oxazepam (internal standard), respectively.

3.2. Validation of the method

3.2.1. Establishment of response function

3.2.1.1. Selection of the appropriate statistical model. The standard least-squares method was used to fit the calibration curve, from responses obtained with the 36 standard concentration preparations. Variance analysis was first performed by the Cochran test. Homogeneity of variances was rejected at the 5% level of signifi-

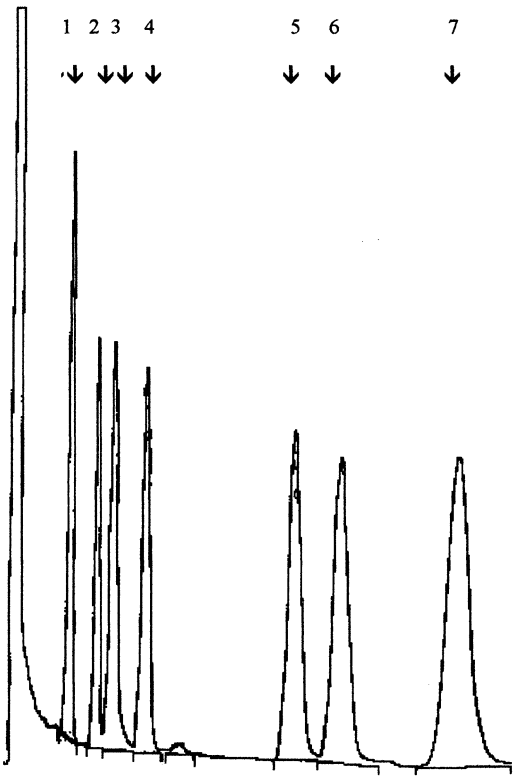

Fig. 2. Chromatogram of AEDs. Legend: 1, 10 hydroxy-CBZ; 2, PBB; 3, epoxy-CBZ; 4, OXC; 5, CBZ; 6, PHT; 7, Oxazepam.

cance if $C > C_{(0.05,5,3)} = 0.7071$ (Table 1). To validate the calibration curve, two possibilities could be used. The regression line could be fitted using the weighted least-squares method or using a simple mathematic transformation. Our choice was a simple linear regression model after a logarithmic transformation. With this logarithm transformation, all the Cochran tests were not significant; variances were homogeneous (Table 1).

Table 1
Cochran test values obtained without and after logarithmic transformation

AED	*C* value with simple linear regression model	*C* value after logarithmic transformation
PBB	0.923	0.402
OXC	0.773	0.336
10OH-CBZ	0.651	–
Epoxy-CBZ	0.887	0.552
CBZ	0.882	0.668
PHT	0.459	0.704

3.2.1.2. Estimation of regression parameters. Slopes (b), intercepts (a) and coefficients of determination (r^2) were estimated by the method of ordinary least-squares after logarithmic transformation (Table 2). Results seem to indicate a good fit with few variations for drugs: CV% = 1.08 for slopes, CV% = 1.7 for intercepts. Variations are more important with CBZ metabolites but always inferior to 10%. All the coefficients of determination were correct: 0.998 or 0.999.

3.2.1.3. Adequacy of the statistical model. Nevertheless, it was necessary to verify the adequacy of the regression model. The adequacy of the linear regression model after logarithmic transformation was based on the lack-of-fit test. The strategy of this test consisted in comparing the lack-of-fit error to the experimental error. The null hypothesis of no lack-of-fit at the 1% level of significance was rejected if F_{exp} (Fisher value obtained with experimental fit) was superior to $F(0.01,12,18) = 3.37$. We failed to reject the null hypothesis of no lack-of-fit, whatever the AED, because the F_{exp} were ranging from 0.246 to 2.563.

3.2.2. Linearity

The confidence intervals for slope of the curve, determined with the concentration of each analyte in the samples and the concentration estimated from the standard curve equation, are reported in Table 3. Confidence limits at the 10% level of significance with 2 degrees-of-freedom were satisfactory, ranging from 0.85 to 1.15. Confidence limits for each analyte were included in this range; therefore, the linearity of each curve was verified.

3.2.3. Precision

The coefficients of variation (CV) for the repeatability (intra-assay variability) and for the intermediary accuracy (sum of intra-assay and inter-assay variabilities) were below the acceptable limit (10%) for the whole concentration range for all the compounds with the exception of 10OH-

Table 2
Regression parameters (mean value ± standard deviation) obtained with three calibration curves

AED	Slope (b)	Intercept (a)	Determination coefficient (r^2)
PBB	1.0002 ± 0.0073	-1.862 ± 0.018	$0.999 \pm 8.1 \times 10^{-5}$
OXC	0.979 ± 0.010	-1.236 ± 0.027	0.999 ± 0.0004
10OH-CBZ	0.171 ± 0.0024	$8.9 \times 10^{-4} \pm 0.069$	0.998 ± 0.0006
Epoxy-CBZ	0.998 ± 0.038	-1.933 ± 0.167	0.999 ± 0.00017
CBZ	0.992 ± 0.006	-1.393 ± 0.038	0.999 ± 0.0002
PHT	0.976 ± 0.017	-3.191 ± 0.039	0.999 ± 0.0002

CBZ and epoxy-CBZ (Table 4). With these two compounds, CV was below 10% for the five upper standard concentrations. The dosage intervals should be revalued thanks to the quantization limit.

3.2.4. Confidence limits of accuracy and quantization limit

Confidence limits of accuracy were estimated at the 10% level of significance. The method acceptance was achieved when confidence limits were included between 80 and 120%. The dosage interval should be revalued thanks to the quantization limits, since the upper confidence limit was out of range, whatever the compound (Table 5).

The accuracy profile allows the estimation of the limits of quantization. The limit of quantization corresponds to the concentration for which the one-side confidence limit of the mean recovery percentage is equal to 120 or 80%. Quantization limits, estimated by this method, were 1.02, 0.58, 3.51, 2.35, 0.66 and 3.13 μg /ml for PBB, OXC, 10OH-CBZ, epoxy-CBZ, CBZ and PHT, respectively.

3.2.5. Absolute recovery

Three levels of concentration were used to determine the absolute recovery. The first one was above the maximal plasma level, the second one was included in the therapeutic window and the third one was below the minimal plasma level. Results are summarized in Table 6.

3.3. Selectivity

Forty psychotic drugs were injected directly in order to underscore potential interferences (Table 7). Co-prescriptions with toloxatone and benzodiazepines need some vigilance for result interpretation. To verify the presence of dosage interferences, the previous products were injected in the chromatograph after treatment. The obtained results confirmed these interferences.

4. Discussion

Although other methods of dosage are described for traditional AEDs as immunological methods essentially used in laboratories screening for drug intoxication, the dosage of newer AEDs, in particular oxcarbazepine, is realized by HPLC. The aim of this study was to perform the simultaneous HPLC dosage of PBB, CBZ, PHT, OXC and 10OH-CBZ, to detect epoxy-CBZ in order to avoid interferences in the determination of PBB plasma levels, and to evaluate its toxic potential. Among the methods described for oxcarbazepine dosage by HPLC, some of them allowed the dosage of both CBZ and its metabolites [12]. Otherwise, simultaneous dosage of PBB, CBZ and PHT was reported earlier. However, the simulta-

Table 3
Lower and upper limits for slope confidence interval

AED	Lower confidence limit	Upper confidence limit
PBB	0.904	1.102
OXC	0.924	1.062
10OH-CBZ	0.958	1.041
Epoxy-CBZ	0.875	1.092
CBZ	0.937	1.032
PHT	0.932	1.090

Table 4
Coefficient of variation (%) for repeatability and intermediary accuracy of the five compounds

	PBB	OXC	10OH-CBZ	Epoxy-CBZ	CBZ	PHT
Repeatability						
C_1	2.04	6.26	3.15	0.59	2.66	0.86
C_2	0.23	6.58	2.75	0.43	1.71	1.25
C_3	1.58	1.10	3.57	0.81	1.53	2.20
C_4	1.58	1.53	5.19	1.39	1.53	1.76
C_5	4.34	1.70	2.97	2.59	3.22	3.17
C_6	4.34	6.02	15.77	10.00	6.74	7.06
Intermediary accuracy						
C_1	4.15	7.44	3.83	1.52	3.17	3.21
C_2	2.94	7.66	3.86	1.94	6.93	3.55
C_3	2.60	4.18	4.23	3.27	3.58	2.73
C_4	2.38	6.23	6.76	4.38	3.71	3.46
C_5	5.20	2.37	3.74	7.69	4.93	3.87
C_6	5.20	7.78	19.97	38.41	8.61	8.05

PBB: C_1, C_2, C_3, C_4, C_5 and $C_6 = 150$, 100, 50, 20, 2 and 0.5 μg/ml, respectively. OXC: C_1, C_2, C_3, C_4, C_5 and $C_6 = 100$, 50, 20, 10, 2 and 0.5 μg/ml, respectively. 10OH-CBZ: C_1, C_2, C_3, C_4, C_5 and $C_6 = 150$, 100, 50, 20, 5 and 0.5 μg/ml, respectively. Epoxy-CBZ: C_1, C_2, C_3, C_4, C_5 and $C_6 = 100$, 50, 20, 10, 5 and 2 μg/ml, respectively. CBZ: C_1, C_2, C_3, C_4, C_5 and $C_6 = 100$, 50, 20, 10, 2 and 0.5 μg/ml, respectively. PHT: C_1, C_2, C_3, C_4, C_5 and $C_6 = 100$, 50, 20, 15, 10 and 2 μg/ml, respectively.

neous dosage of OXC and its active metabolite was not usually described. Wad [13] was the only one to propose a method for the simultaneous dosage of oxcarbazepine, 10-hydroxy carbamazepine and traditional AEDs, but it required a HPLC method by elution gradient. In routine analysis, the main advantage of the isocratic method in comparison with elution method was the sparing of time between the end of measure and the following measure. It was not necessary to wait for the initial condition feedback. This method allowed, with a high selectivity, the detection of six compounds (four drugs and two main metabolites) that are widely coprescribed, i.e. antipsychotics, antidepressants, hypnotics and anxiolytics (Table 7), even if interferences with all metabolites of these drugs cannot be ruled out. Oxazepam seems to be the only coprescription that could interfere in the analysis of results. Nevertheless, in this case, the 5-*p*-methyl phenyl-5-phenyl hydantoïne could be used as the internal standard, but the analysis time would be extended to about 35 min.

The statistical validation of the method assured that, whatever the drug, a linear response could be obtained for a concentration range larger than the therapeutic window. This therapeutic window is not fully defined regarding OXC and 10-hydroxyCBZ, even if the clinical response seems to be correlated to plasma levels [14]. The highest plasma levels were 1 and 7.3 μg/ml for OXC and 10-hydroxy-CBZ, respectively, after one oral administration of 600 mg [15]. After repeated administrations, plasma levels should range from 3 to 20 and 20 to 40 μg/ml for OXC and 10-hydroxy-CBZ, respectively. These concentrations remain higher than the limits of quantization of the method (0.62 and 3.51 μg/ml for oxcarbazepine and 10-hydroxy-CBZ, respectively). The limits of quantization for each analyte after extraction were compatible with AED drug monitoring in routine.

Pienimäki et al. [12], Rouan et al. [15] and Matar et al. [16] reached lower limits of quantization: about 50 ng/ml for oxcarbazepine and between 20 and 25 ng/ml for 10-hydroxycarbamazepine. The first reason to explain a higher limit of quantization in our study is the harsh validation method employed [11]. The second reason is the detection wavelength used. In fact, all the methods described in the literature are based on the spectrophotometric detection around 210 nm. The

Table 5
Lower (LCL) and upper (UCL) confidence limits of accuracy for the five compounds

	PBB		OXC		10OH-CBZ		Epoxy-CBZ		CBZ		PHT	
	LCL	UCL	LCL	UCL	LCL	UCL	LCL	UCL	LCL	UCL	LCL	UCL
C_1	90.43	110.00	81.86	116.63	93.57	106.11	96.67	101.60	90.73	105.36	92.98	108.20
C_2	93.47	107.39	82.34	118.55	94.27	106.99	95.51	101.77	85.57	118.93	94.07	111.21
C_3	94.24	106.52	91.35	111.31	91.69	105.36	93.95	104.59	92.34	109.31	93.00	105.76
C_4	93.14	104.20	86.77	116.60	91.09	113.78	93.73	108.22	91.40	108.92	90.98	107.12
C_5	88.00	112.52	90.29	100.98	89.18	100.83	84.80	109.25	87.05	109.89	87.05	104.50
C_6	88.02	123.95	83.62	121.13	80.51	158.79	38.81	170.48	80.39	121.22	83.49	122.55

See Table 4 for concentrations.

detection around 210 nm should allow dropping the limits of quantization of OXC and its metabolites. However, this wavelength is far from maximum of absorption of PBB and PHT (240 and 258 nm, respectively) and the method sensitivity for these two analytes should be highly decreased with such detection. Moreover, some interference with classic HPLC grade solvents and endogenous plasma components are reported at 210 nm. Nevertheless, the limit of quantization obtained with our study was close to that obtained by Theisohn and Heimann [17], i.e. 0.39 μg/ml for OXC. It is interesting to note that this limit allowed performing a clinical pharmacokinetic study. The choice of the 240 nm wavelength is therefore a compromise to get a correct sensitivity for all the analytes tested.

Table 6
Absolute recoveries (mean value ± standard deviation)

AED	C_1	C_2	C_3
PBB	100.67 ± 3.03	98.54 ± 5.08	96.66 ± 3.45
OXC	106.03 ± 6.88	105.97 ± 5.00	103.45 ± 5.97
10OH-CBZ	100.93 ± 9.53	77.75 ± 9.31	75.61 ± 9.79
Epoxy-CBZ	99.74 ± 7.48	68.92 ± 5.17	115 ± 8.63
CBZ	96.86 ± 0.83	96.41 ± 2.31	96.30 ± 3.70
PHT	99.17 ± 4.10	96.14 ± 0.03	89.93 ± 1.01

PBB: C_1, C_2 and $C_3 = 100$, 20 and 2 μg/ml, respectively. OXC: C_1, C_2 and $C_3 = 100$, 20 and 0.5 μg/ml, respectively. 10OH-CBZ: C_1, C_2 and $C_3 = 150$, 50 and 5 μg/ml, respectively. Epoxy-CBZ: C_1, C_2 and $C_3 = 100$, 10 and 2 μg/ml, respectively. CBZ: C_1, C_2 and $C_3 = 100$, 20 and 0.5 μg/ml, respectively. PHT: C_1, C_2 and $C_3 = 100$, 20 and 2 μg/ml, respectively.

The statistical validation showed a good repeatability (CV below 10%) and a good intermediary precision for the whole concentration range for OXC, PBB, CBZ and PHT and for concentrations C_1–C_5 for 10OH-CBZ and epoxy-CBZ.

Accuracy was satisfactory for the five upper concentrations, whatever the AED. The dosage interval was reduced according to the determination of the quantization limit.

The absolute recoveries were quite excellent, since near from 100%. The recovery reduction of 10OH-CBZ to 84.76% was probably responsible (partially at least) for increase of quantization limit to 3.51μg/ml.

5. Conclusion

Treatment of samples by a simple precipitation, use of a C18 column, detection at 240 nm, allowed obtention of a process easy, cheap and fast (allowing to offset the length of the analysis). This process reduced the risk of mistake during manipulations achieved in the hospital pharmacokinetic laboratory. This method performs the drug monitoring of oxcarbazepine and its metabolites, simultaneously with the AEDs commonly dosed in practice by laboratories of clinical pharmacokinetic. The OXC and 10-hydroxy-CBZ monitoring should underscore some drug interactions and should assess their clinical relevance. This method with the same processing (extraction and chromatography separation) could be used not only for the routine monitoring of PBB, CBZ, and

Table 7
Time of retention of some psychotropic drugs

	Drug	Retention time (min)
Anticonvulsants	Sodium valproate	ND
	Primidone	ND
Imipraminic	Imipramine	ND
Antidepressants	Clomipramine	ND
	Dosulepine	34.41
	Desipramine	ND
	Trimipramine	ND
	Amitryptiline	ND
	Nortriptyline	ND
	Doxepin	ND
	Amoxapine	ND
	Maprotiline	ND
Atypicals	Viloxazine	ND
	Mianserine	ND
	Medifoxamine	ND
	Opipramol	ND
	Demexiptiline	ND
MAOI	Toloxatone	6.68
SSRI	Fluvoxamine	ND
	Fluoxetine	ND
Neuroleptics	Mirtazapine	ND
Phenothiazines	Fluphenazine	ND
	Trifluprom azine	ND
Butyrophenones	Haloperidol	ND
	Pipamperone	ND
Atypicals	Loxapine	ND
	Clozapine	ND
	Desméthylclozapine	ND
	Risperidone	ND
	9-Hydroxy risperidone	ND
Anxiolytics	Olanzapine	ND
Benzodiazepines	Chlorazepate	ND
	Chlordiazepoxyde	30.75
	Clobazam	ND
	Flunitrazepam	33.69
	Bromazepam	9.87
	Diazepam	70.22
	Clonazepam	28.8
	Triazolam	ND
	Lorazepam	29.17
	Loprazolam	ND
	Lormetazepam	ND
Miscellaneous	Alprazolam	ND
	Buspirone	52.56

Two hundred nanograms of compounds were injected. ND: not detected.

PHT, but also for primidone, a prodrug of PBB, or fosphénytoïne.

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