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Monitoring of olanzapine in serum by liquid chromatography–atmospheric pressure chemical ionization mass spectrometry

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Abstract

A selective assay of olanzapine with liquid chromatography atmospheric pressure chemical ionization (LC–APCI–MS, positive ions) is described. The drug and internal standard (ethyl derivative of olanzapine) were isolated from serum using a solid-phase extraction procedure (C_{18} cartridges). The separation was performed on ODS column in acetonitrile–50 m*M* ammonium formate buffer, pH 3.0 (25:75). After analysis of mass spectra taken in full scan mode, a selected-ion monitoring detection (SIM) was applied with the following ions: *m/z* 313 and 256 for olanzapine and *m/z* 327 and 270 for the internal standard for quantitation. The limit of quantitation was 1 μg/l, the absolute recovery was above 80% at concentration level of 10 to 100 μg/l. The method tested linear in the range from 1 to 1000 μg/l and was applied for therapeutic monitoring of olanzapine in the serum of patients receiving (Zyprexa™) and in one case of olanzapine overdose. Olanzapine in frozen serum samples and in frozen extracts was stable over at least four weeks. The examinations of urine extracts from patients receiving olanzapine revealed peaks of postulated metabolites (glucuronide and *N*-desmethylolanzapine).

Keywords: Olanzapine

1. Introduction

Olanzapine, a thienobenzodiazepine, is an antipsychotic agent showing high receptor affinity binding in vitro at serotonin, dopamine, muscarinic and histamine receptors. Olanzapine is indicated for the acute treatment and maintenance of schizophrenia and related psychotic disorders and is usually applied orally in a dose of 5 to 20 mg/day. The drug was characterized by a half life of 27–31 h and distribution volume of 22 l/kg. Olanzapine acts as very weak inhibitor of cytochrome P-450 enzymes (CYP1A2, CYP2D6, CYP2C19 and CYP3A) and is not likely to cause relevant drug–drug interactions [1–4]. The drug was claimed to be safe in therapeutic doses [5–7] and seems not to induce extrapyramidal side-effects.

There are several points indicating the need for monitoring of drug level in serum or plasma during therapy. Perry et al. [8] observed that the clinical response to olanzapine among schizophrenic patients was related to its concentration and a minimum effective concentration of 9 μg/l plasma was found.

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The concentrations of drug in serum showed a tendency to increase with the administered daily oral dose [9]. On the other hand, the data concerning olanzapine concentrations in blood during therapy are still scarce and the therapeutic range was not yet fully established. Samples of plasma from several patients receiving 10 to 20 mg olanzapine daily contained 8 to 31 μg/l of drug [9]. In another study, after administration of 2.5 to 17.5 mg olanzapine daily, the concentrations of 5 to 50 μg/l serum were found [10]. A therapeutic range of 5 to 75 μg/l was recently proposed [11]. Robertson [12] analyzed 1655 serum samples on olanzapine and found mean concentrations of 36 μg/l, 70% of results were below 49 μg/l and 90% below 70 μg/l. Toxicity symptoms occurred at concentrations above 70 μg/l. The pharmacokinetics of olanzapine may be significantly influenced by carbamazepine, an agent often used concomitantly in the treatment of maniac psychotic disorders [13].

Some reports on the acute toxicity of olanzapine and the interpretation of postmortem values appeared recently. In fatal monointoxication with an unknown dose of Zyprexa™, the concentration of olanzapine in blood was 4.9 mg/l and in gastric contents, 41 mg/l [14]. Anderson et al. [15] studied 35 autopsy cases where olanzapine was detected. In two cases fatal olanzapine poisoning was diagnosed, with blood levels of 1.6 and 1.2 mg/l. Jenkins et al. [16] examined autopsy samples taken from the patient treated with olanzapine who died due to natural reasons. The following concentrations were determined: in heart blood 0.550 mg/l, in bile 6.346 mg/l, in gastric content 0.157 mg/l. In the case described by Stephens et al. [17], a suicidal intoxication with olanzapine was ruled after determination of 1.238 mg/l in blood and 6.987 mg/l in urine. Levine et al. [18] examined five autopsy blood samples taken from subjects treated with olanzapine who died due to reasons other than intoxication and found drug levels ranging from 0.04 to 0.27 mg/l. This data indicated that the ''postmortem therapeutic range'' for olanzapine is higher than the reported antemortem data. In six olanzapine associated death cases the concentrations of 0.19 to 1.24 mg/l in postmortem blood and 0.024 to 3.53 mg/l in vitreous humor were observed [19]. In none of these cases was olanzapine poisoning ruled.

In the case of acute olanzapine overdose, gas chromatography with nitrogen detection was usually used. This method, however, was less suitable for therapeutic drug monitoring (TDM) due to limited sensitivity; the reported limits of quantitation ranged from 3 μg/l [11,12] through 25 μg/l [15] up to 100 μg/l [16]. Catlow et al. [10] applied HPLC with electrochemical (coulometric) detection (HPLC–EC) for TDM of olanzapine. The drug was extracted from plasma with mixed-phase SPE cartridges. Olanzapine was quantified using ethyl homologue (LY170222). The limit of detection (LOD) of 0.25 μg/l was reported. The same method was applied for determination of olanzapine and its hydroxymethyl- and desmethyl-metabolite in rat plasma [20]. Aravagiri et al. [9] isolated olanzapine from plasma with liquid–liquid extraction and determined by HPLC–EC. The LOD was also 0.25 μg/l. The method was applied for therapeutic drug monitoring. Olesen and Linnet [21] described a HPLC procedure with separation on normal-phase silica column and UV detection at 270 nm. Ascorbic acid was added to the serum as a stabilizing agent (antioxidant) before solvent extraction. The instability of olanzapine at 4°C was reported by Levine et al. [18] who observed a drop from 0.98 mg/l to 0.16 mg/l after one month storage of blood samples. Berna et al. [22] recently published a liquid chromatographic–tandem mass spectrometric procedure (LC–APCI–MS–MS) for quantitation of olanzapine in serum. The drug was isolated with solid-phase extraction cartridges. A linear range from 0.25 to 50 μg/l was found.

Extensive studies on disposition and biotransformation of olanzapine in humans, performed with application of electrospray LC–MS, LC–MS–MS, GC–MS, NMR and radiochemical method, demonstrated that 10-*N*-glucuronide is the main olanzapine metabolite. *N*-oxidation, *N*-desmethylation and 4-*N*-glucuronidation was also observed [23]. In contrast to these findings, the animals (mice, dogs and rhesus monkeys) were not able to form appreciable amounts of 10-*N*-glucuronide [24].

The purpose of the present study was to develop a simple and specific method for therapeutic olanzapine monitoring in serum, using solid-phase extraction (SPE) and liquid chromatography–atmospheric pressure chemical ionization mass spectrometry (LC–APCI–MS). This technique is used routinely in our laboratory for determination of various drugs of abuse and other psychoactive

substances [25–28]. Also, an attempt was undertaken to identify postulated olanzapine metabolites in serum and urine samples.

2. Experimental

2.1. Reagents and materials

Olanzapine (LY170053, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b] [1,5]benzodiazepine) and internal standard (IS) (LY170222, 2-ethyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b] [1,5]benzodiazepine) were supplied by Eli Lilly and Company (Indianapolis, IN, USA).

SPE cartridges Bond Elut C_{18} 200 mg were purchased from Varian GmbH (Darmstadt, Germany). The cartridges were rinsed with 1 ml of methanol, 1 ml of water and 2 ml of 0.01 *M* ammonium carbonate buffer (pH 9.3) before use.

2.2. Sample preparation

The same solid-phase extraction method was applied, which was successfully used for various other basic drugs, like opiates and their glucuronides, synthetic opiate agonists, cocaine and its metabolites and flunitrazepam [25–28]. One milliliter serum or urine was vortex-mixed with 2 ml of 0.01 *M* ammonium carbonate buffer (pH 9.3) and with I.S. (50 ng per sample). After 10 min centrifugation at 5000 *g*, 2 ml of clear supernatant were applied on SPE cartridge and slowly passed through it (ca. 5 min). The SPE cartridge was rinsed with 2 ml of 0.01 *M* ammonium carbonate buffer (pH 9.3) and vacuum dried for 5 min. The retained drugs were eluted under gravity force with 2×0.5 ml of methanol–0.5 *M* acetic acid (9:1) to 1 ml Eppendorf tubes containing 5 μl 0.001 *M* HCl and dried under nitrogen at 37°C. The residue was reconstituted in 100 μl of HPLC mobile phase and centrifuged 4 min at 14000 *g*. 5–20 μl of clear supernatant was injected into LC–MS.

2.3. HPLC

For olanzapine monitoring the separation was performed using Superspher RP 18 columns (E. Merck, Darmstadt, Germany), 125 mm long, 3 mm ID, 4 μm particle size. A mixture of acetonitrile (ACN) and 50 m*M* ammonium formate buffer (AMF), pH 3.0 (25:75) was used as mobile phase at the flow-rate of 0.3 ml/min. For the examination of postulated olanzapine metabolites in serum and urine a gradient elution was applied (initial mobile phase: ACN–AMF 10:90, in 5 min to ACN–AMF 25:75, 5 min at 25:75) at the flow-rate of 0.5 ml/min.

2.4. APCI–MS

A SSQ 7000 single quadrupole instrument (Finnigan MAT, San Jose, CA, USA) with atmospheric pressure chemical ionisation (APCI) source was used in positive ionization mode. The following APCI inlet conditions were applied: sheath gas (nitrogen) pressure 70 p.s.i., auxiliary gas (nitrogen) 20 ml/min, heated vaporizer temperature 450°C, heated capillary temperature 190°C, corona current 5 μA. In order to establish the appropriate selected ion monitoring (SIM) conditions, the full scan mass spectra of olanzapine and I.S. were taken in the range of 50 to 350 amu at octapole offset values of 10, 20, 30 and 40 V. The increase of octapole offset voltage was associated with higher acceleration of ions and consecutive fragmentation (in-source collision-induced dissociation). For these experiments loop injections of single pure drugs (50 ng each in 5 μl mobile phase), without HPLC separation, were applied.

On the basis of observed fragmentation (Figs. 1 and 2) the octapole offset voltage was set at 20 V for SIM detection of drug and I.S. The following ions were monitored: m/z 313 and 256 (protonated molecular peak and fragment of olanzapine), and m/z 327 and 270 (protonated molecular peak and fragment of I.S.). The quantitation of olanzapine in serum was done from the peak areas of molecular peaks of drug and I.S. The presence of fragment peaks was used for confirmation purposes. Blank serum samples spiked with olanzapine to the concentrations of 1, 5, 10, 50 and 100 μg/l each were used as calibration standards for routine olanzapine determinations in clinical samples. This concentration range covered all values found in clinical samples. The concentration of internal standard was always 50 μg/l.

The study on metabolites was done in full scan mode in the range of 100 to 500 amu, using scan

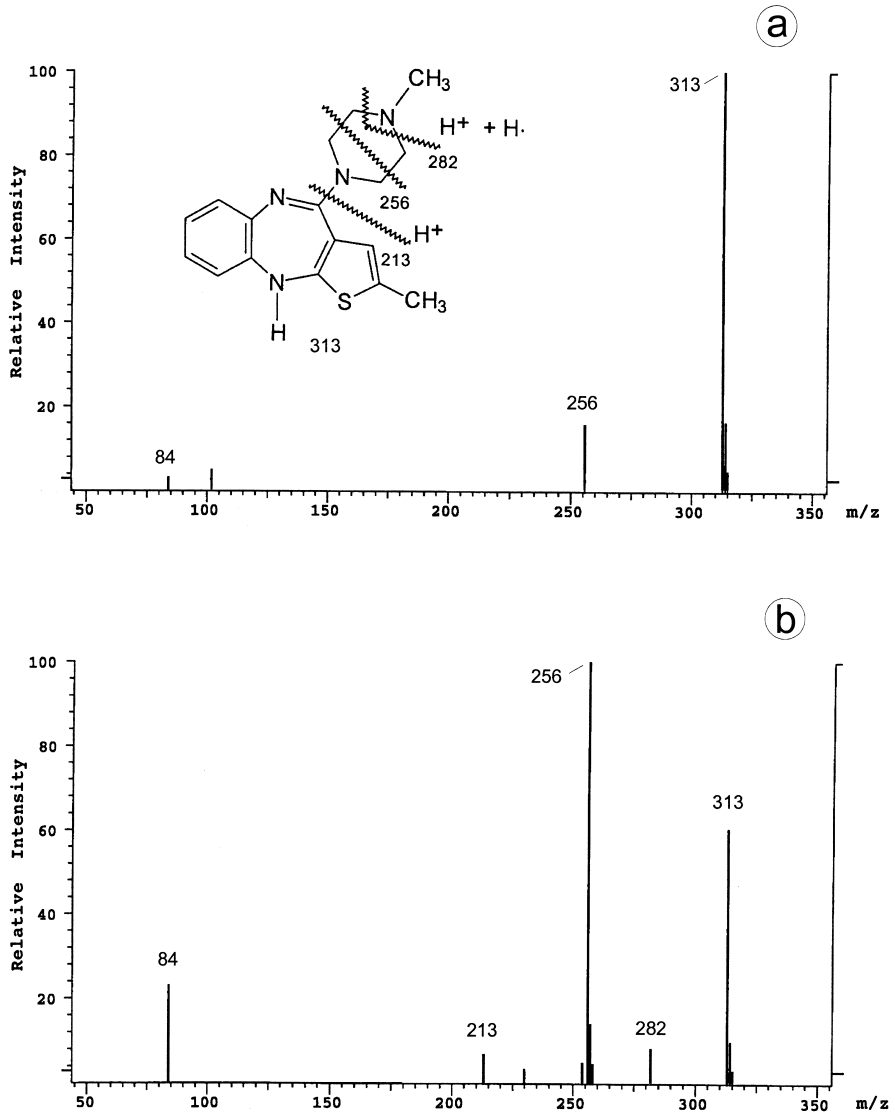

Fig. 1. Mass spectra of olanzapine taken at octapole offset values of 10 V (a) and 20 V (b). Scan range m/z 50–350 amu.

time of 1 s and octapole offset values of 10 V and 30 V. The same conditions were applied for selectivity study.

2.5. Validation standards

For validation a pooled human serum from a local blood bank was used. Serum samples were spiked with olanzapine in the concentration range of 0.5, 1, 5, 10, 50, 100 and 1000 μg/l and stored at −20°C until extraction. These samples were prepared independent of the calibration standards.

The validation was based on the guidelines established during the conference on method validation for the quantitation of drugs in biological media [29]. According to these guidelines, the within-day precision was determined at three concentration levels (5, 10 and 50 μg/l), the day-to-day precision was studied during five different days at five concentrations (1, 5, 10, 50 and 100 μg/l), the acceptable

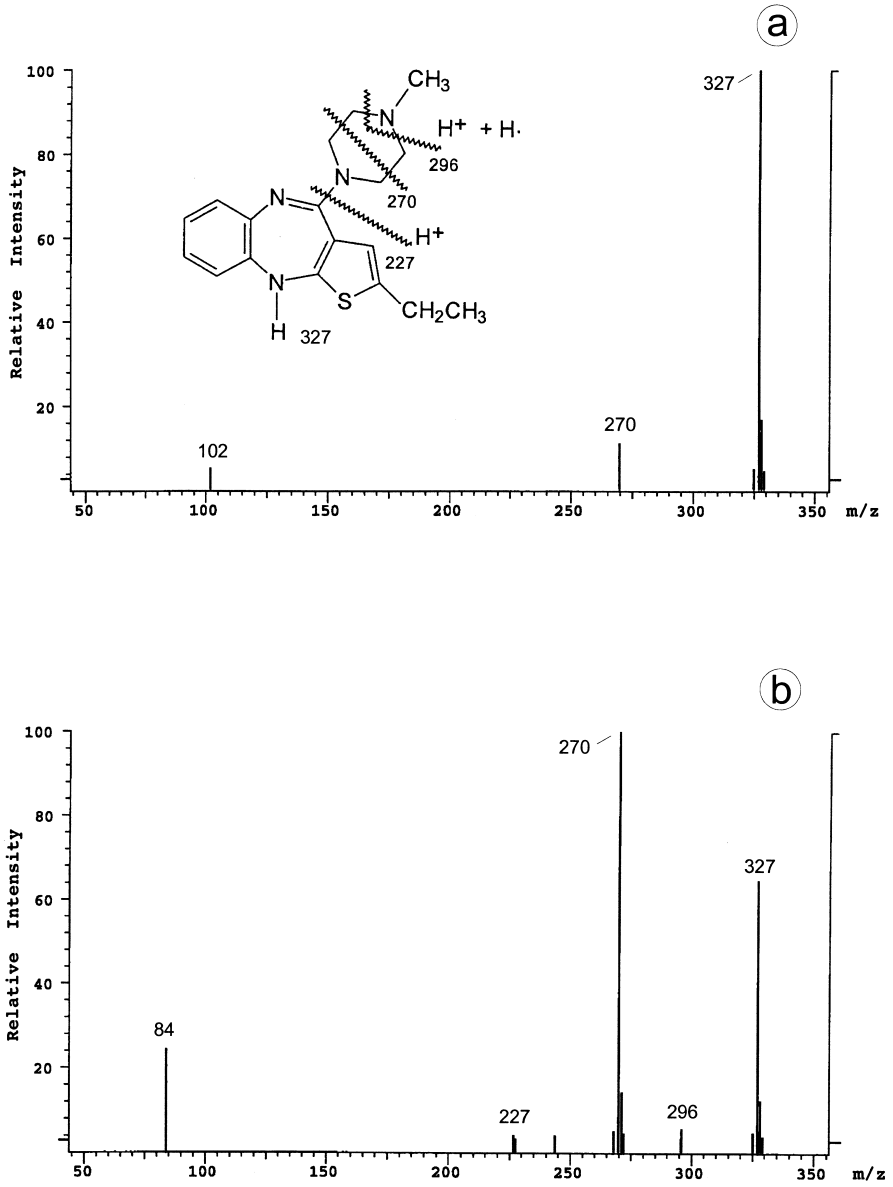

Fig. 2. Mass spectra of LY170222 (olanzapine internal standard) taken at octapole offset values of 10 V (a) and 20 V (b). Scan range m/z 50–350 amu.

coefficient of variation (C.V.) at the concentration corresponding to the limit of quantitation was estimated at 20%, whereas at higher concentrations the variability of precision and accuracy should not exceed 15% C.V. Absolute analytical recovery was tested in triplicate at the concentration levels of 10, 50 and 100 μg/l and was defined as percent peak areas of corresponding amounts of olanzapine spiked post-extraction to blank serum extract. The concentration range chosen for recovery study corresponds the range usually observed in serum samples of olanzapine-treated patients.

Table 1
Validation data

Day		1 μg/l	5 μg/l	10 μg/l	50 μg/l	100 μg/l
1.	Rec.[a]			84±4.6	87±3.6	86±6.6
	Acc.[b]	108	101	98	97	96
	Pr.[c]	18	8	7	6	5
2.	Rec.			82±3.1	86±4.2	81±3.8
	Acc.	110	103	101	99	97
	Pr.	17	9	6	5	4
3.	Rec.			84±7.0	85±3.6	88±1.9
	Acc.	112	106	100	98	95
	Pr.	19	10	7	6	5

[a] Rec.=absolute recovery (mean±SD from three determinations).
[b] Acc.=calibration accuracy %.
[c] Pr.=calibration precision %.

2.6. Selectivity study

Psychiatric patients, receiving olanzapine, were usually medicated with other drugs, like e.g. phenothiazine derivatives, carbamazepine, clozapine or fluvoxamine. In order to check the possible analytical interferences, serum samples of five patients subjected to olanzapine therapy were examined in full scan mode. Also, serum samples of five patients treated with clozapine, thioridazine, fluvoxamine and dibenzepine were examined without any addition and after spiking with olanzapine to the concentration of 10 μg/l.

2.7. Clinical samples

Serum samples taken from the patients medicated with olanzapine (Zyprexa™) were subjected to analysis. Blood samples were taken at least 12 h after the last olanzapine dose and 1 h before the next dose from patients who were given olanzapine at least one week long. Therefore, trough levels of drug in steady state were determined. Up to now, olanzapine levels were monitored in nine patients and three to five determinations were performed in each case. This allowed assessment of the intra-individual variability of drug concentrations. Blood samples were also taken from one patient 3 and 12 h after alleged ingestion of 30 tablets Zyprexa™ (150 mg olanzapine). This patient was admitted to hospital with mild signs of intoxication.

2.8. Stability study

Due to the reports on the instability of olanzapine [18,21], blood samples were centrifuged within 1 h after sampling and serum was stored at −20°C until analysis. Reconstituted extracts were frozen again after analysis and re-examined two more times within one month. Also, olanzapine was determined four times in five frozen serum samples within one month.

2.9. Search for possible olanzapine metabolites

Four urine samples and four serum samples taken from patients receiving olanzapine were examined in full scan mode. Gradient elution was applied.

3. Results and discussion

3.1. Mass spectra of olanzapine and I.S.

Full-scan mass spectra of olanzapine and LY170222 (IS), taken at increasing octapole offset voltages, showed gradually progressing fragmentation of the molecule (Figs. 1 and 2). The fragmentation proposals are depicted in these figures. Since at octapole offset value of 20 V both the protonated molecular ions of olanzapine and I.S. (m/z 313 and 327) and their characteristic fragments (m/z 256 and 270) showed high abundance, this value was selected

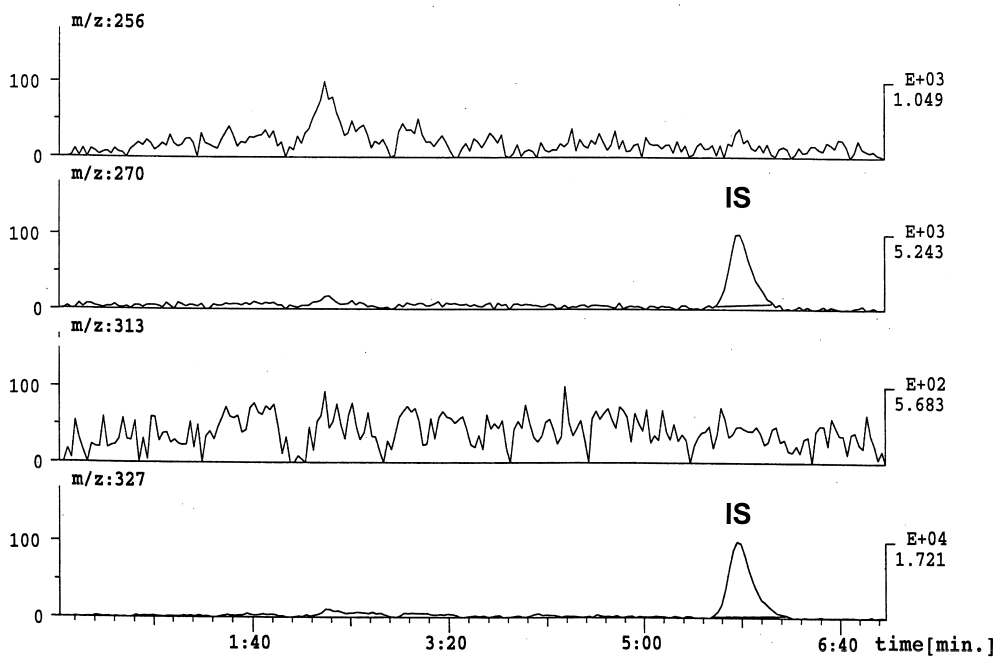

Fig. 3. Mass SIM-chromatogram of blank serum extract, spiked with internal standard (IS).

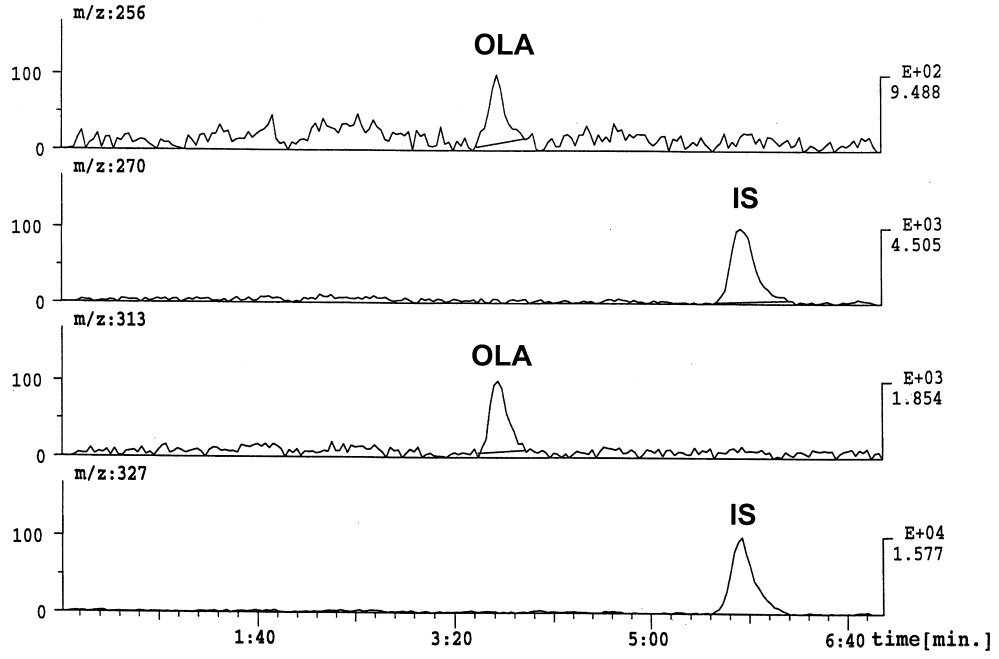

Fig. 4. Mass SIM-chromatogram of serum extract, spiked with olanzapine (OLA) to the concentration of 1 μ/l and with internal standard (IS).

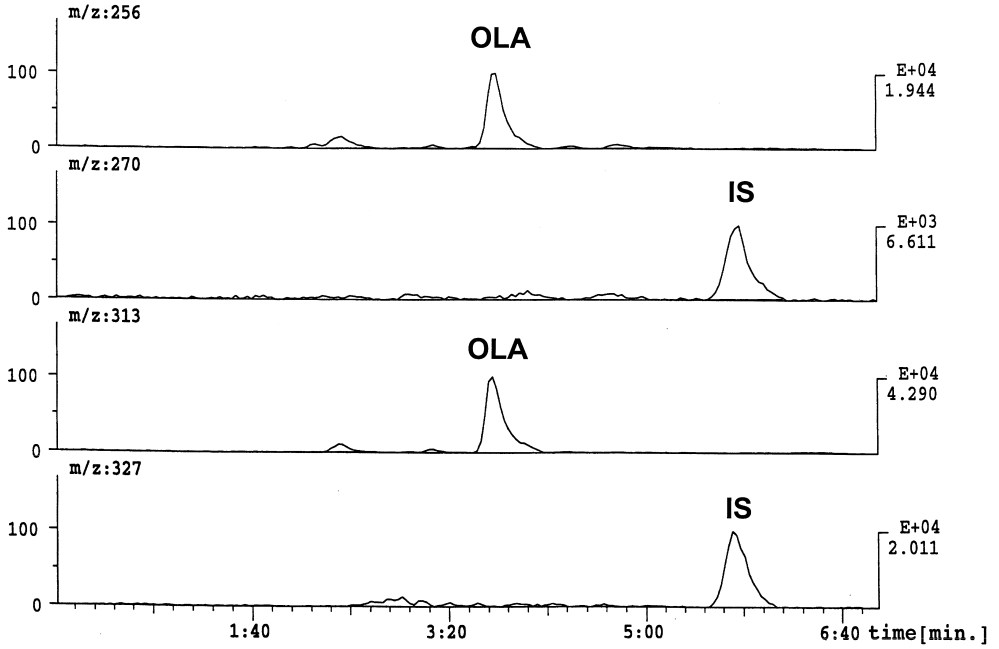

Fig. 5. Mass SIM-chromatogram of serum extract, taken from patient during olanzapine therapy. The olanzapine concentration was 25 μg/l.

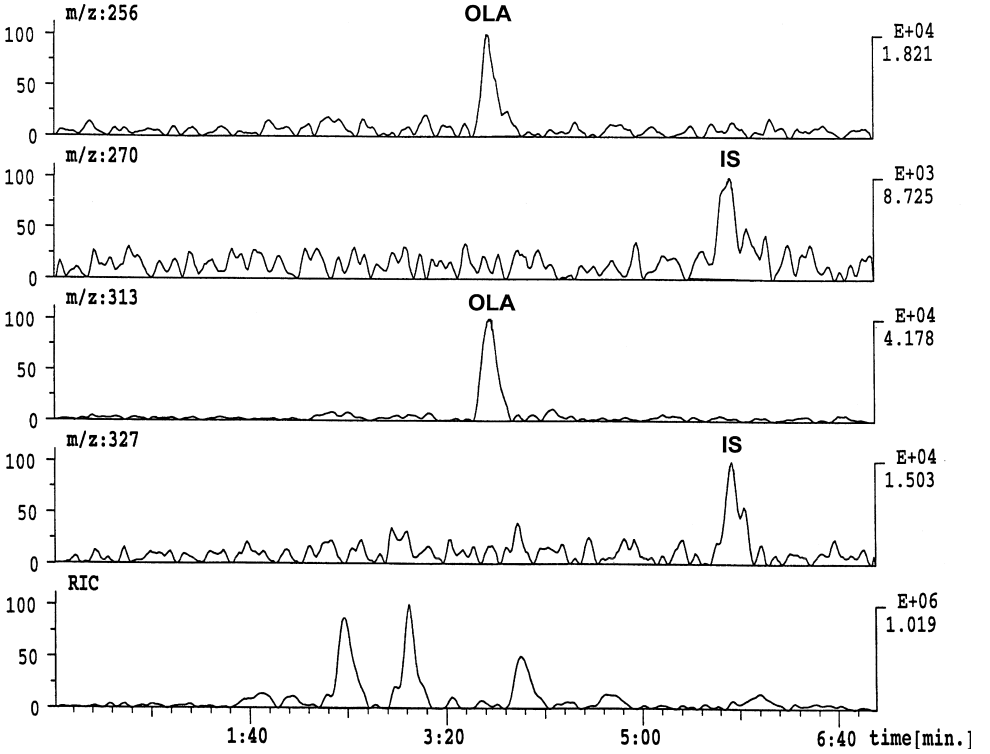

Fig. 6. Full scan mass chromatogram (m/z 100–500 amu) of the same serum extract as in Fig. 5. This patient received also clozapine and fluvoxamine.

for SIM procedure used for olanzapine quantification.

3.2. Validation

The validation was performed in three series, using serum samples spiked with olanzapine to the concentration of 0.5, 1, 5, 10, 50, 100 and 1000 μg/l. The results are summarized in Table 1. For recovery experiments, the concentrations of 10, 50 and 100 μg/l were used. The limit of quantitation was 1 μg/l. The precision of determination at this level was 18% RSD, fulfilling the recommendations published elsewhere [29]. The standard curve for olanzapine was linear over the range of 1–1000 μg/l, had a regression coefficient of 0.9997, a slope of 0.01902, an x intercept of −1.137, a standard deviation from regression line 0.02429. The limit of quantitation observed is adequate to the therapeutic concentration range of olanzapine [9–11]. Figs. 3–5 show the chromatograms of blank serum, of serum spiked with olanzapine to the concentrations of 1 μg/l and of serum taken from patient receiving olanzapine. The examination of serum samples spiked with olanzapine alone to the concentrations of 1000 μg/l each showed no peak corresponding to I.S. Also, the same experiment performed with I.S. alone revealed no peaks corresponding to olanzapine. Therefore, the mutual mass contribution of both substances, affecting the quantitation, may be excluded.

3.3. Selectivity of the assay

Five serum extracts of patients receiving olanzapine and other drugs were examined in full scan mode. In no case were the mass peaks, interfering with the relevant masses observed. Fig. 6 shows the full scan mass chromatogram of serum sample, taken from a patient receiving olanzapine, fluvoxamine and clozapine. On the other hand, serum extracts obtained from the patients treated with clozapine, fluvoxamine, thioridazine and dibenzepine showed no peaks, which might possibly interfere with olanzapine determination.

Table 2
Results from patients receiving olanzapine (1–5) and from one intoxicated person (6)

Patient[a]	Day of therapy	Dose Mg=mg/kg	Other drugs mg/day	*C* ng/ml
1	36	15=0.17	Dibenzepine 225, Thioridazine 200	37
1	66	30=0.32	″	45
1	67	″	″	32
1	68	″	″	35
1	71	″	″	73
2	150	10=0.15	Carbamazepine 800	68
2	153	20=0.30	″	28
2	154	″	″	42
2	156	″	″	28
2	163	″	″	81
3	27	10=0.18	Fluvoxamine 175	179
3	33	″	″	91
3	34	″	″	127
3	46	15=0.27	″	29
4	30	20=28	Thioridazine 230, Fluphenazine 12, Propranolol 60	43
5	231	7.5=0.10	Citalopram 40	88
6	3 h after ingestion	150=1.9	-	885
6	12 h after ingestion	150=1.9	-	422

[a] Mean values: Patient; 37±5, Patient 2; 49±24, patient 3; 93±62.

Table 3
Olanzapine levels in serum and serum extract stored at −20°C and analyzed several times. The results are presented as percent of initial value

	Day 5	Day 15	Day 30
Serum (n=5)	97±8	–	99±7
Extract (n=5)	101±7	97±8	100±6

3.4. Samples from patients

The method was applied for TDM of olanzapine in serum samples taken from psychiatric patients receiving Zyprexa™. The results of these determinations are showed in the Table 2. The intraindividual variability of drug levels, measured in three persons, were relatively high and amounted to 15%, 49% and 66% RSD. These results are similar to data obtained by Aravagiri et al. [9], who observed intra-individual variations between 10% and 92%. No correlation between administered drug dose (mg/kg) and olanzapine concentration was observed. It must be stressed, that all patients also received several other drugs, which may alter olanzapine metabolism and affect the serum levels. In one case of olanzapine overdose, a distinctly higher concentration was observed (885 μg/l), which was accompanied by dizziness and slurred speech. After the next 9 h, the olanzapine concentration dropped to 422 μg/l and all symptoms disappeared.

The study on olanzapine stability showed no relevant changes in drug concentration over one month of storage at −20°C (Table 3). During this period, serum samples were subjected to three freeze-thaw cycles and extracts to two such cycles. It seems that this simple mode of storage is sufficient and the addition of stabilizers, e.g. ascorbic acid [21] is not necessary. Our results are concordant with the data of Chiu et al. [20], who observed no changes in

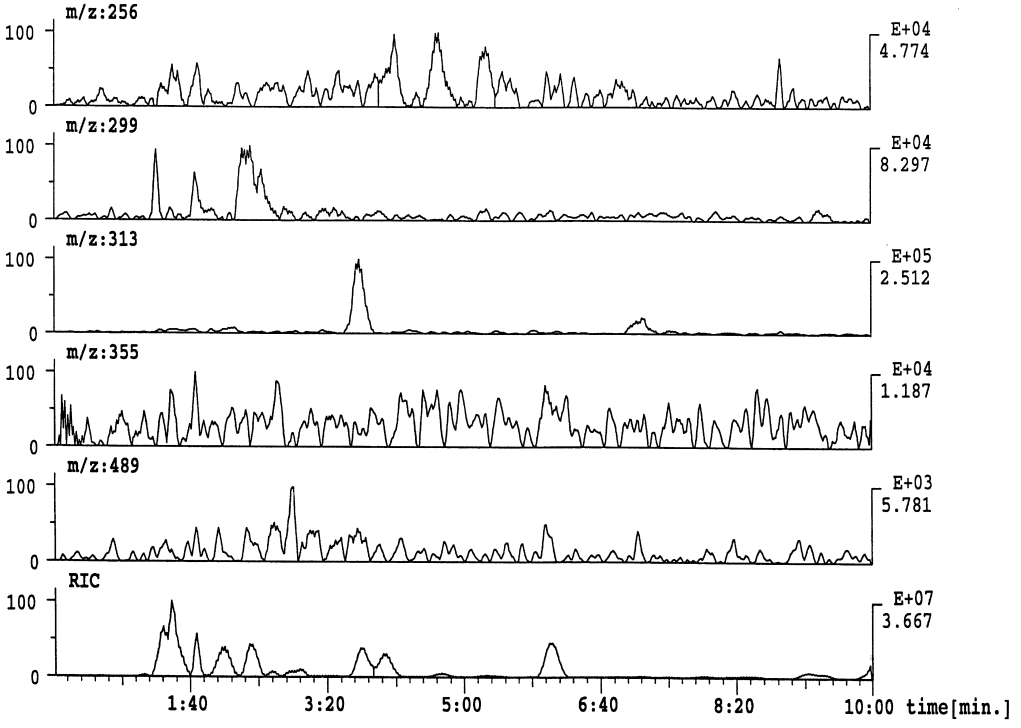

Fig. 7. Full-scan mass chromatogram (m/z 100–500 amu) of blank urine extract, taken in gradient elution conditions. Ion traces relevant for olanzapine and metabolites are shown.

olanzapine levels during 19 weeks of storage at −70°C.

3.5. Search for olanzapine metabolites

Four urine and four serum samples, taken from patients receiving olanzapine, were extracted without addition of I.S. and subjected to LC–MS examination in full-scan mode in gradient elution conditions. Two blank urine samples were also analyzed. The samples were analyzed at octapole offset value of 10 V and 30 V, in order to confirm the identity of substances through collision-induced dissociation. Unfortunately, the reference standards of olanzapine metabolites (olanzapine-10-*N*-glucuronide, *N*-desmethylolanzapine, 2-OH-olanzapine) were not available for these experiments. The only possible source of the metabolites (Eli Lilly and Company) declined to provide us with the reference standards. In this situation, the peaks of substances with masses corresponding to olanzapine metabolites cannot be unequivocally identified. However, in all urine samples taken from olanzapine patients the peaks at *m*/*z* of 489 (corresponding to olanzapine-10-*N*-glucuronide) and *m*/*z* 299 (corresponding to *N*-desmethylolanzapine) were observed. These peaks were not visible in the blank urine extracts. Moreover, by increasing the fragmentation energy from 10 V to 30 V, the peak at *m*/*z* 489 revealed enhanced fragmentation to *m*/*z* 355 and 313. The mass *m*/*z* 355 was described by Berna et al. [22] as a fragment of olanzapine-10-N-glucuronide, and the mass *m*/*z* 313 may be interpreted as olanzapine aglycone. Also the expected fragmentation of olanzapine molecule to *m*/*z* 256 at 30 V was observed. Figs. 7–9 show the mass chromatograms of blank urine extracts as well as extracts of urine extracts from olanzapine patient analyzed at octapole offset voltage of 10 V and 30 V,

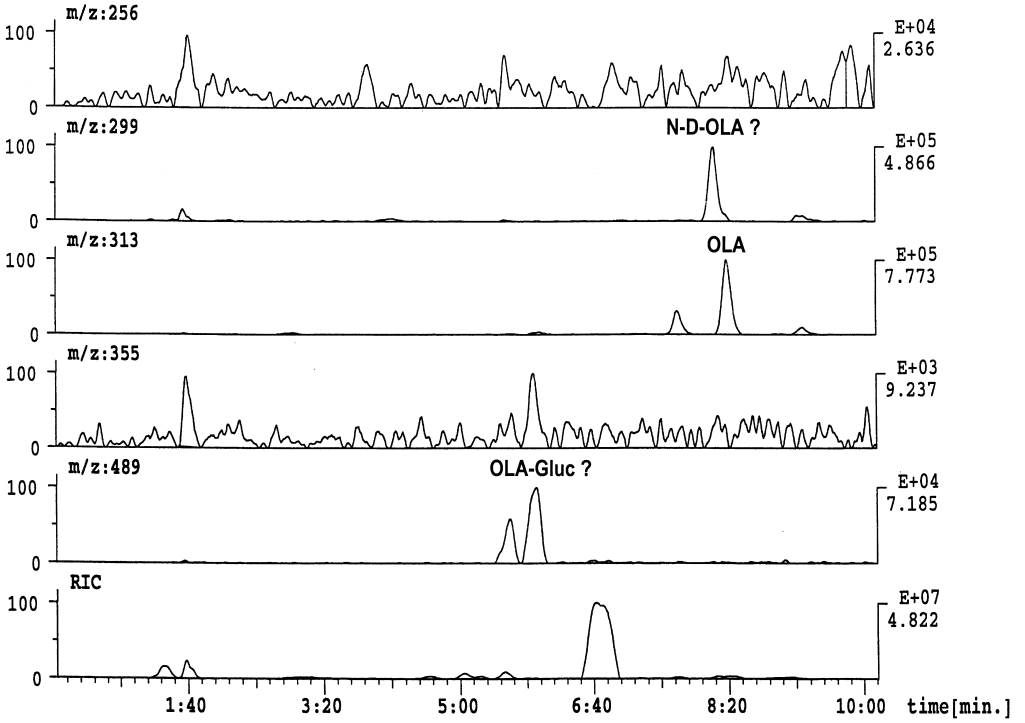

Fig. 8. Full-scan mass chromatogram (*m*/*z* 100–500 amu) of urine extract from the patient receiving olanzapine. Ion traces relevant for olanzapine and metabolites are shown. Octapole offset value: 10 V. The peak *m*/*z* 313, Rt 8:20 was identified as olanzapine (OLA). The peak *m*/*z* 489, Rt 6:00 may correspond to olanzapine-10-*N*-glucuronide (OLA-Gluc), the peak *m*/*z* 299, Rt 8:10 to *N*-desmethyl-olanzapine (N-D-OLA).

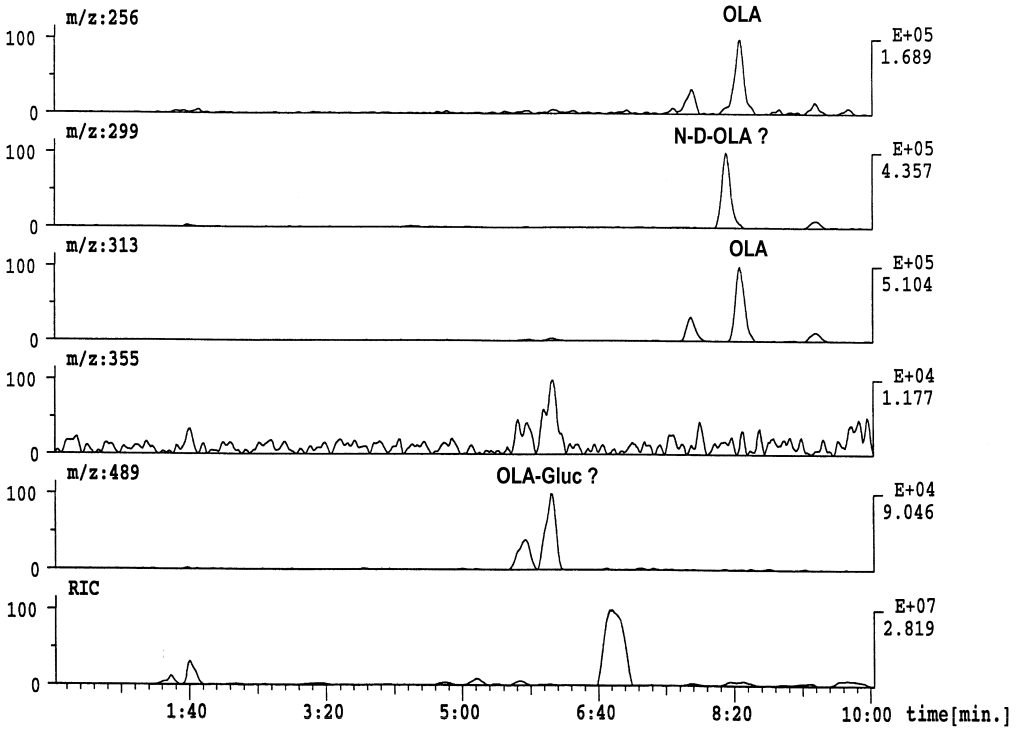

Fig. 9. Full-scan mass chromatogram (m/z 100–500 amu) of the same extract as in the Fig. 8, taken at octapole offset value of 30 V. The fragmentation of olanzapine (OLA) is visible.

respectively. No peaks corresponding to postulated metabolites were found in the serum samples. From the observations of Chiu and Franklin [20] and Kasahun et al. [23] it is obvious, that desmethyl and hydroxy metabolites of olanzapine occur in serum in low concentrations. Hence, the presented method may be a good starting point for the determination of olanzapine metabolites. Further work in this direction will be continued when the metabolite reference standards are available.

4. Conclusions

The presented method of olanzapine determination fulfils the requirements of therapeutic drug monitoring concerning sensitivity, selectivity and simplicity. The solid phase extraction procedure applied appeared very universal, which makes possible simultaneous determinations of several alkaline drugs of clinical relevance in small amount of serum. Sample preparation steps may be easily automated. LC–APCI–MS is a robust and flexible method, allowing not only the dedicated, selected-ion-monitoring quantitation of analyte, but may easily be applied also to the search of other compounds, e.g. metabolites. Since a new generation of low-cost, bench top LC–MS instruments, both in electrospray and APCI options, is finding its way to clinical chemistry labs, this technique will certainly be often used in the field of therapeutic drug monitoring.

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