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Simultaneous determination of levomepromazine, midazolam and their major metabolites in human plasma by reversed-phase liquid chromatography

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Abstract

A sensitive and reliable high-performance liquid chromatographic (HPLC) assay is a prerequisite for pharmacokinetic analysis of continuous infusion of levomepromazine adjuvant to midazolam. We developed such a method to determine the levels of levomepromazine, midazolam and their major metabolites (levomepromazinesulfoxide, desmethyl-, didesmethyl-levomepromazine, *O*-desmethyllevomepromazine and α-hydroxy-midazolam) simultaneously. Desmethylclomipramine was used as an internal standard (I.S.). The lower limit of quantification of this assay was set for levomepromazine 4.1 μg/l, levomepromazinesulfoxide 4.9 μg/l, *O*-desmethyllevomepromazine 18.4 μg/l, α-hydroxymidazolam 26.6 μg/l, midazolam 23.4 μg/l, didesmethyllevomepromazine 15.8 μg/l, and desmethyllevomepromazine 6.6 μg/l. The between- and within day assay variations were commonly below 5%. The recovery in human plasma for the different analytes varied between 85 and 11%. The accuracy of this assay varied between 95 and 105% for the different concentrations. The linearity of this assay was set between 25 and 800 μg/l (r^2>0.999 of the regression line). The first results of pharmacokinetic analysis of midazolam indicated that half-life varied between 1.1 and 1.9 h. Pharmacokinetic analysis using a one-compartment model of levomepromazine revealed that the apparent volume of distribution was 4.1±2.4 l per kg lean body mass and the metabolic clearance was 309±225 l per hour per 70 kg. This assay proved to be robust and reproducible. It can reliably be used for further study of the pharmacokinetics of continuous infusion of levomepromazine.

Keywords: Levomepromazine; Midazolam

1. Introduction

Sedation is an integrated part of patient care management in the Intensive Care Unit (ICU), especially in anxious and agitated patients. Sedation regimes on the ICU include the use of benzodiazepines, opioids and propofol. Nevertheless, no satisfactory sedation can be achieved in all patients due to intolerance or an a priori contraindication for some of those sedatives. Therefore, extension of the sedative armamentorium by use of phenothiazines,

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for example levomepromazine, could be of use in insufficiently sedated patients [1]. Levomepromazine has infrequently been used as an adjuvant to the infusion of midazolam in mechanical ventilated ICU patients. As the effects of subcutaneous, intramuscular or oral administration can be unpredictable, continuous intravenous administration is preferred [2]. However, no official registration for intravenous levomepromazine has been available.

The sedative properties of levomepromazine have been described previously in terminal (cancer) care and burn patients [1]. The sedative effects of levomepromazine are histaminergic mediated [3]. Suggestions have been made that the metabolites of levomepromazine, especially *N*-desmethyllevomepromazine, could enhance or be responsible for the sedative properties of levomepromazine [4]. *N*-Desmethyllevomepromazine was found to have adjuvant effects on the muscle relaxation properties of levomepromazine [5]. In rats, beside sedative properties, this metabolite revealed an 80% dopaminergic receptor activity (muscle relaxation) compared to levomepromazine [4]. The pronounced central effects of this metabolite were also suggested in another study [6]. Due to the pharmacodynamic properties of levomepromazine and its metabolites, levomepromazine may contribute to an optimal level of sedation leading to a better tolerance of enduring stressful events like mechanical ventilation in the ICU. Levomepromazinesulfoxide, another major metabolite, has been studied because of the relative high serum concentrations [4,7], but no significant pharmacological activity has yet been determined. Urine analysis of psychiatric patients revealed 3- and 7-hydroxylevomepromazine (as glucuronide metabolites), but no pharmacological activity of these compounds was recorded [8], and will therefore not be validated.

Previously developed analytical methods for levomepromazine are not suitable for routine application, because of time consuming sample preparation [9]. However, for reliable pharmacokinetic (PK) and pharmacodynamic (PD) studies, a validated analytical method for routine applications was mandatory [9–11]. Pharmacokinetic studies of orally and intramuscularly administered levomepromazine have been published, but as far we know no data are available of continuous infused levomepromazine in ICU patients [4,7,8,12–18]. Therefore, we developed a rapid HPLC assay for routine quantification of levomepromazine, *N*-desmethyl-levomepromazine, *N*-di-desmethyllevomepromazine, *O*-desmethyl-levomepromazine, levomepromazinesulfoxide, midazolam and α-hydroxymidazolam simultaneously. Midazolam and α-hydroxymidazolam are analysed because of (frequent) concomitant administration of levomepromazine

2. Materials and methods

2.1. Chemicals and reagents

Levomepromazine, *N*-desmethyllevomepromazine, *N*-didesmethyllevomepromazine, levomepromazine-sulfoxide and *O*-desmethyllevomepromazine were generously provided by Aventis Pharma (Hoevelaken, The Netherlands). α-Hydroxymidazolam and midazolam were purchased from Roche (Mijdrecht, The Netherlands). Acetonitrile, methanol, *n*-heptane, iso-amylalcohol, phosphoric acid, sodium-hydroxide and potassiumdihydrogenphosphate (all analytical quality) were purchased from Merck (Darmstadt, Germany). Stock solutions were prepared with freshly distilled water. Blank plasma was obtained from pooled donor plasma (Viecuri Medical Centre, Venlo, The Netherlands).

2.2. Preparation of standard solutions

Stock solutions (1 mg/ml) of all analytes and the internal standard (I.S.) were prepared by dissolving the accurately weighted amount of analyte in methanol. The stock solutions were stored at −20 °C. For preparation of calibration concentrations of 10–1600 μg/l, appropriate amounts of diluted stock solutions were added to pooled blank plasma. Extraction of analytes was performed with 2.00 ml plasma, diluted with 400 μl of 1 *M* NaOH solution and 50 μl of I.S. solution. Five millilitres of heptane-isoamylalcohol (98:2 v/v) was added. The samples were shaken for 25 min at 350 shakes per minute (s.p.m.). The organic phase was evaporated with N_2 gas at 40 °C. The residue was dissolved in 100 μl mobile phase, a solution of 0.1 *M* potassiumdihydrogenphosphate,

pH 3.5 with 17% of phosphoric acid–acetonitrile (70:30 v/v) The flow-rate was 1.3 ml/min. The injector loop volume, 60 μl, of standard solutions was injected and analysed at 250 nm.

2.3. Chromatographic system

The HPLC system (Waters Chromatography, Etten-Leur, The Netherlands) consisted of the following components: photodiode array detector (PDA 996), 600 E system controller, 610 Fluid Unit isocratic pump and 717-plus autosampler. The analytical column was a Symmetry C8 (150×3.9 mm I.D.), 100 Å, 5 μm. The guard column was a Symmetry C8 Sentry™ Guard (20×3.9 mm i.d), 100 Å, 5 μm. All analyses were carried out at ambient temperature. The Millennium[32] software package, version 3.05.01, was used for integration processes.

2.4. Validation procedures

Spiked pooled blank plasma samples were used in the validation procedures. All samples were performed six times. The between day assay and within day assay variation were calculated by ANOVA. Calculation of the between day variation was performed with four independent sample sets. Twenty blanks were assayed. The mean peak height and its standard deviation of the blank signal were used to calculate the lower limit of detection (LLOD) and the lower limit of quantification (LLOQ). The LLOD was defined as the lowest quantity that reliably could be differentiated from the background level in this case with a signal-to-noise ratio (s/n) of at least 3. The LLOQ was defined with a signal-to-noise ratio of 10. The recovery of each concentration was determined by comparing the peak heights of the spiked plasma samples following the extraction procedure and spiked mobile phase samples. Samples in spiked mobile phase were performed three times. Samples of spiked plasma were performed six times.

Statistical analysis was performed using MS-Excel® SR-2 1997 (Microsoft Amsterdam, The Netherlands) and SPSS® release 10.0.7 2000 (SPSS Inc. Chicago, IL, USA).

Table 1
Drugs tested for interference (concentration of 1 mg/l)

Acetaminophen	Diclofenac	Naproxen
Amiodaron	Disopyramide[b]	Nefazodone
Amitriptyline[a]	Doxepine	Nortriptyline[g]
Bupivacaine	Phenytoine	*N*-Propionylprocainamide
Carbamazepine	Flecainide[c]	*O*-Desmethylvenlafaxine
Clobazam	Flunitrazepam	Oxazepam[g]
Clonazepam	Flurazepam[d]	Paroxetine
Clozapine[d]	Fluvoxamine	Phenobarbital
Codeine	Ibuprofen	Pipamperon
Coffeinum	Imipramine[f]	Prilocaine
Desalkylflurazepam	Lidocaine	Sulfamethoxazol
Desethylamiodaron	Lorazepam	Temazepam
Desipramine[e]	Lormetazepam	Theophylline
Desmethylclozapine	Maprotiline	Valproic acid
Desmethyldiazepam	Mono-OH-carbazepine	Venlafaxine
Desmethyldoxepine	*N*-Acetylprocainamide	Verapamil
Desmethylmaprotiline[f]		
Diazepam		

[a] Metabolite of amitriptyline, nortriptyline does interfere with desmethyllevomepromazine.
[b] Interferes with levomepromazinesulfoxide.
[c] Interferes with α-hydroxymidazolam.
[d] Interferes with *O*-desmethyllevomepromazine.
[e] Interferes with di-desmethyllevomepromazine.
[f] Interferes with desmethyllevomepromazine.
[g] Interferes with levomepromazine.

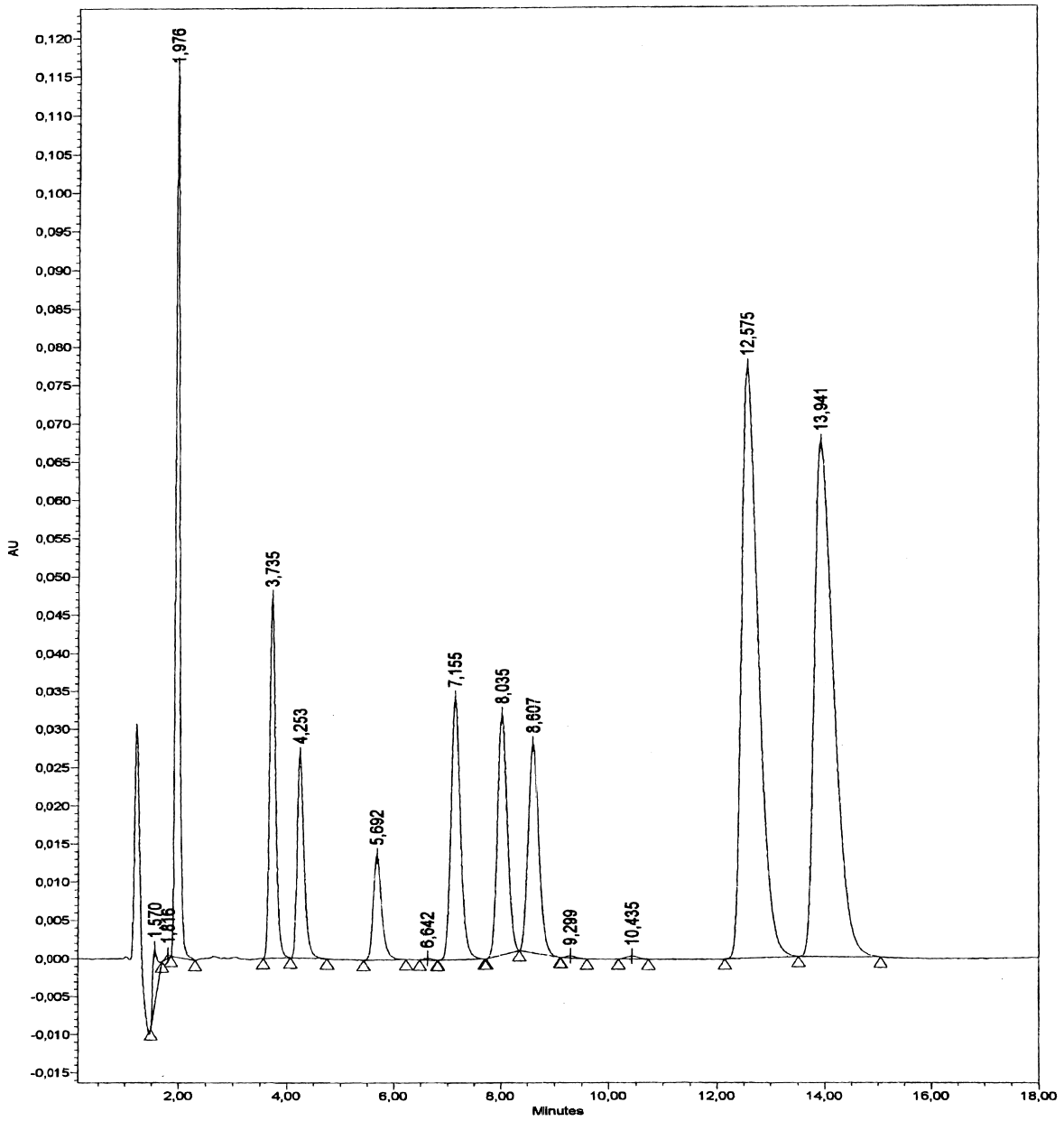

Fig. 1. A representive chromatogram of levomepromazine, midazolam and their major metabolites.

Retention time (min)	Analyte
1.976	LMSO
3.735	O-DMLM
4.253	MID
5.692	AHMID
7.155	DDMLM
8.035	DMLM
8.607	LM
12.575	DMCLOM[a]
13.941	CLOM[b]

LMSO=levomepromazinesulfoxide. O-DMLM=O-desmethyllevomepromazine. MID=midazolam. AHMID=α-hydroxy midazolam. DDMLM=N-di-desmethyllevomepromazine. DMLM=N-desmethyllevomepromazine. LM=levomepromazine. [a] Desmethylclomipramine (I.S.). [b] Internal control clomipramine in case of interference of drugs with desmethylclomipramine.

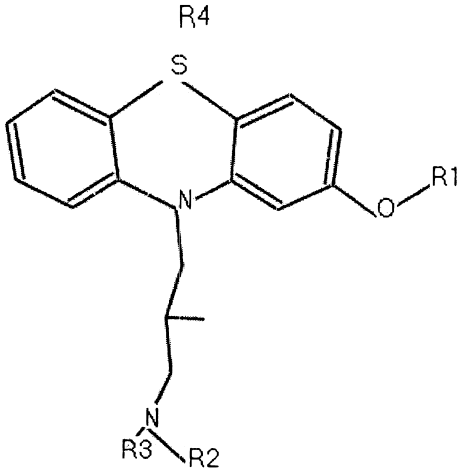

Fig. 2. Molecular structure of levomepromazine and its major metabolites (structures are derived from Loennechen et al. [10]). Levomepromazine: R1=CH_3, R2=CH_3, R3=CH_3 and R4= Levomepromazinesulfoxide: levomepromazine and R4=O N-desmethyllevomepromazine: levomepromazine and R2=H N-didesmethyllevomepromazine: levomepromazine and R2=H and R3= H O-desmethyllevomepromazine: Levomepromazine and R1=H.

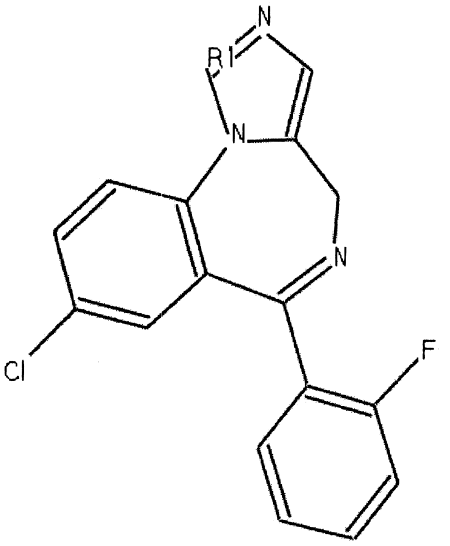

Fig. 3. Molecular structure of midazolam and α-hydroxymidazolam.
Midazolam: R1=CH_3
α-Hydroxymidazolam: R1=CH_2OH.

2.5. Selectivity

From the HPLC drug library drugs were selected with a retention time (±10%) equal to the validated compounds. Drugs that are not used in general in the ICU were not tested further. The selected possible interfering drugs (Table 1) were injected in the prescribed chromatographic system (1 mg/l: stock solutions in methanol, diluted with mobile phase). Drugs with the same retention time were spiked in blank plasma and prepared as samples. Interference is defined as any peak with the same retention time of the validated compounds in the same chromatographic system (including extraction method and UV detection).

2.6. Pharmacokinetic study

The study was approved, according to the declaration of Helsinki, by the local ethic committee.

Table 2
Within day assay variation (%), calculated by ANOVA for levomepromazine, midazolam and their major metabolites

Conc. (μg/l)	LM[1]	LMSO[2]	*O*-DMLM[3]	DMLM[4]	DDMLM[5]	MID[6]	AHMID[7]
10	3.7	3.3	nr	nr	nr	–	–
25	1.7	2.1	2.6	nr	1.9	–	–
50	2.2	2.2	2.8	2.2	3.0	1.3	1.3
100	1	2.4	1.6	0.9	2.3	2.7	2.6
200	2.8	3.1	2.7	3.0	3.5	1.6	1.4
400	1.6	2.5	2.5	1.3	1.9	8.6	5.9
800	1.7	3.1	3.4	1.6	2.1	2.6	2
1600	–	–	–	–	–	2.7	2.8

1, levomepromazine; 2, levomepromazinesulfoxide; 3, *O*-desmethyllevomepromazine; 4, *N*-desmethyllevomepromazine; 5, *N*-di desmethyllevomepromazine; 6, midazolam; 7, α-hydroxymidazolam; Nr, not reliable, see Table 4; –, not tested.

Table 3
Between assay variation (%), calculated by ANOVA for levomepromazine, midazolam and their major metabolites

Conc. (μg/l)	LM[1]	LMSO[2]	*O*-DMLM[3]	DMLM[4]	DDMLM[5]	MID[6]	AHMID[7]
10	44.8[a]	6.2	nr	nr	nr	–	–
25	5.5	4.8	4.8	nr	8.2	–	–
50	5.1	3.3	2.7	4	3.4	10.1	7.7
100	6.7	2.7	3.6	4	1.9	6.5	3
200	2.7	2.3	1.7	3.2	0.7	4.3	1.2
400	0.7	1.2	0.7	0.2	0.6	6.9	2
800	0.2	0.4	0.3	0.2	0.1	0.8	0.5
1600	–	–	–	–	–	0.3	0.2

1, levomepromazine; 2, levomepromazinesulfoxide; 3, *O*-desmethyllevomepromazine; 4, *N*-desmethyllevomepromazine; 5, *N*-di desmethyllevomepromazine; 6, midazolam; 7, α-hydroxymidazolam; nr, not reliable (see Table 4); –, not tested.
[a] Above limit of quantification (see Table 4).

Patients insufficiently sedated with midazolam (0.15 mg/kg per h) were evaluated for adjuvant levomepromazine therapy. Exclusion criteria were age below 18 years or age above 70 years, serum transaminases or alkaline phosphatase levels above twofold the upper limit of the normal value, concommittant amiodaron administration and pregnancy. Withdrawal from the study took place in the case of severe liver dysfunction. Two EDTA tubes of 5.4 ml of whole blood were collected at the following time intervals after start of levomepromazine therapy (2 mg i.v. bolus followed by 0.03 mg/kg per h): 0, 0.5, 1, 2, 4, 8, 12, 24 and after 48 h. Sulfoxidation by erythrocytes of phenothiazines and phenothiazine metabolites may occur at ambient temperature [19,20]. Therefore, all samples were centrifuged immediately after collection and the plasma was stored at −20 °C until analysis. The stability of midazolam was tested. No degradation of midazolam and metabolites was found (unpublished data). Pharmacokinetic analysis was performed with one-compartmental analysis (MW\Pharm®, Mediware, Groningen, The Netherlands).

Table 4
Lower limit of detection (LLOD) and lower limit of quantification (LLOQ) in μg/l for levomepromazine, midazolam and their major metabolites

	LLOD (μg/l)[a]	LLOQ (μg/l)[b]
LM[1]	3.7	4.1
LMSO[2]	4.3	4.9
O-DMLM[3]	15.2	18.4
DMLM[4]	6.1	26.6
DDMLM[5]	13.3	15.8
MID[6]	22.7	23.4
AHMID[7]	25.6	26.6
DMCLOM[8]	3.9	4.0
CLOM[9]	11.7	23.6

1, levomepromazine; 2, levomepromazinesulfoxide; 3, *O*-desmethyllevomepromazine; 4, *N*-desmethyllevomepromazine; 5, *N*-di desmethyllevomepromazine; 6, midazolam; 7, α-hydroxymidazolam; 8, desmethylclomipramine (I.S.); 9, internal control clomipramine in case of interference of drugs with desmethylclomipramine.
[a] LLOD, lower limit of detection, calculated with the mean peak height and its standard deviation of 20 blank samples. The LLOD was defined as the lowest quantity that could be reliably differentiated from the background level in this case with a signal-to-noise ratio of at least 3.
[b] LLOQ, lower limit of quantification, calculated with the mean peak height and its standard deviation of 20 blank samples. The LLOQ was defined as the lowest quantity that could be reliably quantitated from the background level, in this case with a signal-to-noise ratio of at least 10.

3. Results

Fig. 1 shows a representative chromatogram with the retention times of all validated drugs, metabolites and internal standards. In Figs. 2 and 3 molecular structures of levomepromazine, midazolam and their major metabolites are presented.

The linearity of the assay, expressed as the correlation coefficient of the regression line [$r^2 > 0.9995$ ($P < 0.001$)], was for levomepromazine and levomepromazinesulfoxide in the range 10–800 μg/l and for other metabolites in the range 25–800 μg/l, and for midazolam and α-hydroxymidazolam in the

Table 5
Extraction ratios in % for levomepromazine, midazolam and their major metabolites

Conc. (μg/l)	LM[1]	LMSO[2]	*O*-DMLM[3]	DMLM[4]	DDMLM[5]	MID[6]	AHMID[7]	DMCLOM[8]
25	77.7	49.7	10.9	71.6	48.6	67.4	52.7	32
50	78.9	49.2	10.5	73.6	58.8	69.2	55.4	32.7
100	84.8	52.5	11.2	78.6	59.5	73.1	59.5	34.9
200	78.9	50.8	11.7	79.9	65.7	71.3	58.3	34.5
400	66.9	41.5	9.5	66.5	55.7	58.2	48.2	28.9

1, levomepromazine; 2, levomepromazinesulfoxide; 3, *O*-desmethyllevomepromazine; 4, *N*-desmethyllevomepromazine; 5, *N*-di desmethyllevomepromazine; 6, midazolam; 7, α-hydroxymidazolam; 8, desmethylclomipramine (I.S.).

Table 6
Accuracy in % for levomepromazine, midazolam and their major metabolites

Conc. (μg/l)	LM[1]	LMSO[2]	*O*-DMLM[3]	DMLM[4]	DDMLM[5]	MID[6]	AHMID[7]
10	95	100	–	–	–	–	–
25	95	99	102	102	101	–	–
50	95	97	101	96	102	105	104
100	96	98	92	95	99	102	100
200	102	101	102	101	102	98	98
400	103	101	99	101	101	97	100
800	99	100	100	100	100	100	99
1600	*	*	*	*	*	100	100

1, levomepromazine; 2, levomepromazinesulfoxide; 3, *O*-desmethyllevomepromazine; 4, *N*-desmethyllevomepromazine; 5, *N*-di desmethyllevomepromazine; 6, midazolam; 7, α-hydroxymidazolam; –, below lower limit of quantification; *, not tested.

range 50–1600 μg/l. The within day and between day assay variations for all analytes and concentrations are given in Tables 2 and 3, respectively. All within day variations are below 6%, with one exception of midazolam at 400 μg/l (8.6%). The between day variation for all tested compounds in all tested concentrations was below our laboratory accepted value of 20%. The between day assay variation of levomepromazine at 10 μg/l was 44.8%, possibly due to an artefact.

The results of the limit of detection and quantification and the extraction ratios of all drugs including their metabolites are presented in Tables 4 and 5, respectively. Data of accuracy are presented in Table

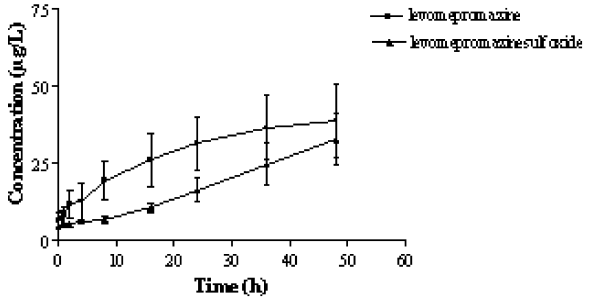

Fig. 4. Concentration versus time curve (mean of 5 patients).

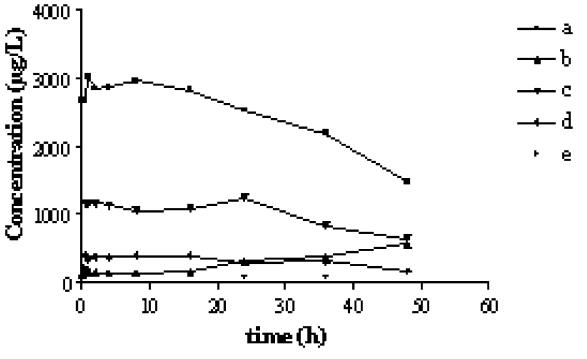

Fig. 5. Midazolam curves for 5 patients.

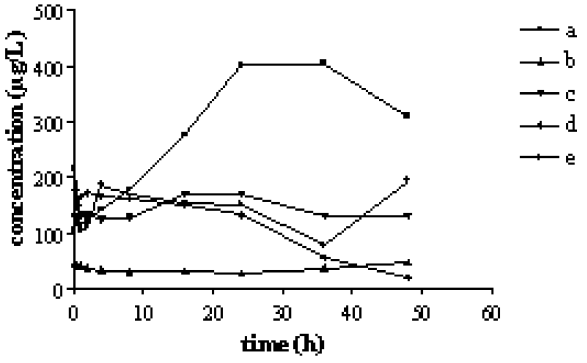

Fig. 6. α-Hydroxymidazolam curves for 5 patients.

6. To assess interference, nine compounds were prepared in blank plasma and assayed under the previously described conditions (Table 1). Phenytoin and phenobarbital have an equal retention time with one of the validated drugs or metabolites. However, due to the used extraction procedure these compounds do not show any interference. Other frequently used drugs on the ICU such as catecholamines, antibiotics, and diuretics have not been tested because either these drugs do not show absorption at 250 nm, or they cannot be extracted with this extraction procedure or differ in retention time compared to the drugs and metabolites assayed.

Plasma curves of five representative patients

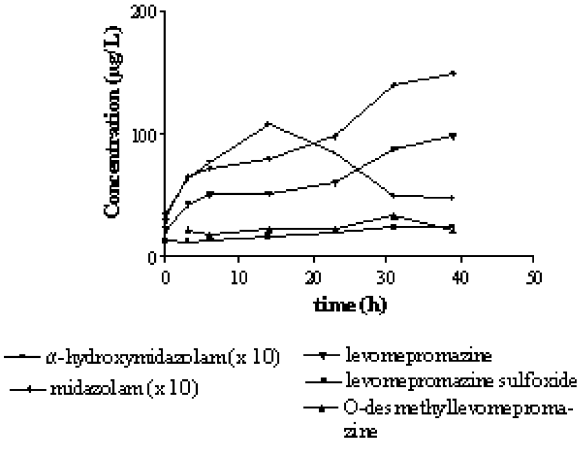

Fig. 7. Time versus concentration of drugs and metabolites in a patient with renal disfunction after start of levomepromaine.

of levomepromazine, levomepromazinesulfoxide, midazolam, and α-hydroxymidazolam are presented in Figs. 4–7, respectively. In Fig. 4 the means are presented because of similar dosing per kilogram, while Figs. 5–7 present the results per patient because of differences in dosing (Tables 7 and 8). Plasma concentrations of levomepromazine, levomepromazinesulfoxide, *O*-desmethyllevomepromazine, midazolam and α-hydroxymidazolam of a patient with renal dysfunction are presented in Fig. 8. The characteristics of five included patients are presented in Table 7. In Table 8 pharmacokinetic parameters of midazolam in four of these patients (the data of one patient were not eligible for pharmacokinetic analysis), fit to a population model of Mould et al. [21], are presented. Preliminary results of pharmacokinetic modelling for levomepromazine are presented in Table 9. An optimum was found with a Bayesian one-compartmental model, with Clm=309±252 l/h per 70 kg lean body mass and V=4.1±2.4 l/kg lean body mass.

4. Discussion

This recently developed HPLC assay appears to be a rapid, sensitive, selective and reliable method for the determination of levomepromazine, midazolam and their major metabolites in human plasma. Accurate data of sensitivity of levomepromazine assays have never been published before.

As the range of sedative drugs is limited in ICU patients, old class drugs such as levomepromazine may reveal special interest to intensivists when used with new indications like continuous intravenous administration as adjuvant in sedation therapy. However, assessment of PK/PD relationships should precede studies in which these relationships might be correlated with the clinical base of sedation. Ideally plasma concentrations may control and forecast the level and duration of sedation to optimise treatment of ICU patients. In our opinion this rapid and accurate assay may greatly facilitate such studies.

Using this assay, levomepromazine, midazolam and their major metabolites in human plasma can be measured reliably over a wide range of serum concentrations: levomepromazine and levomeprom-

Table 7
Patient characteristics of five included patients

Patient code	A	B	C	D	E
Gender	M	F	M	F	M
Age (years)	62	46	65	28	46
Length (cm)	170	177	175	175	180
Mean weight (kg)[a]	88	95	114	70	60

[a] Weight includes positive or negative fluid balance during therapy.

Table 8
Pharmacokinetics of midazolam of the selected patients

Patient code	B	C	D	E
Mean dose (mg/h)	6.1	6.8	0.87	2.52
Cl (ml/min)	48.7	13.0	19.8	82.1
V (l)	122.4	35.7	55.1	132.7
$T_{1/2}$ (h)	1.74	1.91	1.93	1.12

Bayesian fitting was performed using MW/Pharm with a one-compartmental model for a mean dose of 0.07 mg/kg per h, according to Mould et al. [21].

azinesulfoxide in the range 10–800 μg/l, other levomepromazine metabolites in the range 25–800 μg/l and midazolam and α-hydroxymidazolam in the range 50–1600 μg/l. The limit of detection and quantification for this assay are well below the normal serum concentrations of levomepromazine and its metabolites [4]. It may be of paramount importance, especially in patients with decreased clearance rates due to hepatic and/or renal failure, to measure pharmacologically active metabolites reliably. The accuracy of the assay varied between 95 and 105% for different concentrations for different analytes. These results are well acceptable.

Serum concentrations for levomepromazine in psychiatric patients are mainly between 10 and 90 μg/l [4] and the therapeutic plasma concentrations for midazolam are usually above 80 μg/l. The linearity of the validated range of this assay seems to be sufficient for undiluted sample collection for ICU patients.

Despite the low extraction ratios of levomepromazinesulfoxide and *O*-desmethyl-levomepromazine (Table 5), the between day and within day variations of these metabolites are reproducible, and so is the extraction procedure.

This assay is a modification of our standard assay for tricyclic antidepressants. Only a few numbers of compounds have been shown to interfere with this

Table 9
Preliminary results of pharmacokinetic modelling with levomepromazine of the selected patients

Patient code	A	B	C	D	E
Mean dose (mg/h)	2.02	1.87	3.86	1.2	1.53
Cl (l/h)	361	391	166	309	691
V (l)	368	437	261	289	515
$T_{1/2}$ (h)	0.71	0.77	1.09	0.65	0.52

An optimum was found with a Bayesian model using MW/Pharm with a one-compartmental model with Clm=309±252 l/h per 70 kg lean body mass and V=4.1±2.4 l/kg lean body mass.

assay: disopyramide, flecainide, fluvoxamine, nortryptaline (and therefore amitrityline), imipramine, desipramine, clozapine and flurazepam (Table 1). However, these drugs are not frequently used on the ICU.

Pharmacokinetics of midazolam and levomepromazine can be well established using this assay. However, the number of patients included until now is far from sufficient for a reliable pharmacokinetic model. Despite the fact that the optimum was found for a one-compartment model, a two-compartment model seems physiologically more appropriate for central acting drugs like levomepromazine.

In summary this assay can be used for reliable and simultaneous concentration measurements of levomepromazine, midazolam and their major metabolites in human plasma. The individual plasma concentrations of these compounds in ICU patients makes pharmacokinetic modelling possible and are challenging to predict levels and duration of sedation with the combined use levomepromazine and midazolam.

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