Contents lists available at ScienceDirect

Journal of Pharmaceutical Analysis

Original Research Article

Quantification and pharmacokinetic study of tumor-targeting agent MHI148-clorgyline amide in mouse plasma using liquid chromatography-electrospray ionization tandem mass spectrometry

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A B S T R A C T

A high-performance liquid chromatography-electrospray ionization tandem mass spectrometric (HPLC-ESI-MS/MS) method was developed for the quantification of MHI148-clorgyline amide (NMI-amide), a novel tumor-targeting monoamine oxidase A inhibitor, in mouse plasma. The method was validated in terms of sensitivity, precision, accuracy, recovery and stability and then applied to a pharmacokinetic study of NMI-amide in mice following intravenous administration. NMI-amide together with the internal standard (IS), MHI-148, was extracted by protein precipitation using acetonitrile. Multiple reaction monitoring was used for quantification of NMI-amide by detecting m/z transition of 491.2–361.9, and 685.3–258.2 for NMI-amide and the IS, respectively. The lower limit of quantification (LLOQ) of the HPLC–MS/MS method for NMI-amide was 0.005 μg/mL and the linear calibration curve was acquired with R^2 > 0.99 in the concentration range of 0.005–2 μg/mL. The intra- and inter-day precisions of the assay were assessed by percentage of the coefficient of variations, which was within 9.8% at LLOQ and 14.0% for other quality control samples, whereas the mean accuracy ranged from 86.8% to 113.2%. The samples were stable under storage and experimental conditions. This method was successfully applied to a pharmacokinetic study in mice following intravenous administration of 5 mg/kg NMI-amide.

1. Introduction

Monoamine oxidase A (MAOA) is a mitochondria-bound enzyme that degrades monoamine neurotransmitters such as serotonin, dopamine, norepinephrine, and dietary mono-amines [1,2]. Recent studies showed that increased MAOA level is correlated with the prostate cancer progression and poor treatment outcome. Pharmacological inhibition of MAOA reduces the growth of prostate cancer cells in vitro and tumor xenografts in vivo [3–5]. MAOA inhibitors have long been used clinically as anti-depressants; they target either the central nervous system or peripheral tissues where MAOA is present. A tumor cell targeting MAOA inhibitor is highly desirable, as it could achieve better efficacy with less toxicity. A novel tumor-targeting MAOA inhibitor, MAOA-near-infrared (MAOA-NIR) dye conjugate, was synthesized in Shih and Olenyuk laboratories and it showed targeting efficacy in prostate tumor xenograft mouse model following intratumoral and intraperitoneal routes of administration. NIR imaging of the whole body in vivo and individual tumor and normal organs ex vivo showed its localization only in the tumors of the experimental animals. Treated mice showed significant delays in tumor growth and decreases in tumor weight as compared to control mice [6].

Subsequently, an improved version of this molecule was synthesized by combining a tumor-targeting NIR dye MHI-148 (Fig. 1) with a moiety of the MAOA inhibitor clorgyline by an amide bond. The resulting compound, MHI148-clorgyline amide (NMI-amide, Fig. 1), a new near-infrared monoamine oxidase inhibitor, was found to preferentially accumulate in the cancerous lesions and inhibit tumor growth in a human xenograft model [7].

Pharmacokinetic studies are necessary to characterize the plasma concentration profile following drug administration and
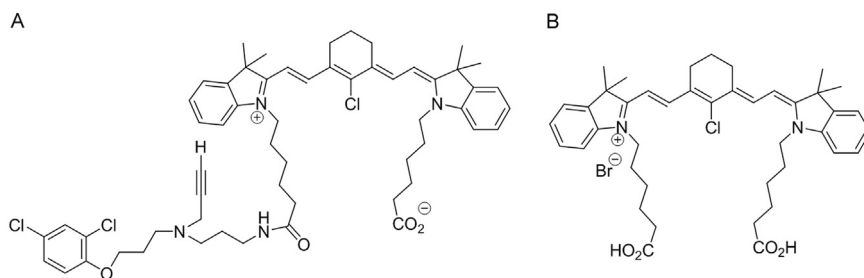
Fig. 1. Chemical structures of (A) NMI-amide and (B) MHI-148 (IS).

this information will be useful for further preclinical and clinical development of this novel anticancer agent. Chromatographic approaches have been most frequently used for quantification of the chemical compounds in plasma samples for pharmacokinetic studies. At present, only radioactive labeled based assay methods have been reported for the assay of clorgyline [8]. MHI-148 has been widely used for cancer detection and the acquisition of real-time pathophysiological information [9]. However, no chromatography based assay methods have been reported for the quantification of clorgyline or MHI-148 in plasma samples. In order to detect NMI-amide in plasma, a UV detector or a fluorescence detector can be potentially used, since NMI-amide has a maximum UV absorbance at 400 nm and a maximum emission wavelength at 808 nm. This is the first report of using mass spectrometry to detect the MHI dye imaging agent and its derivative (NMI-amide) in the plasma samples with high sensitivity and specificity.

Thus, a sensitive and specific high-performance liquid chromatography–mass spectrometric (HPLC–MS/MS) method was developed and validated in terms of accuracy, precision, reproducibility, and recovery. This method was applied to a pharmacokinetic study following intravenous administration of 5 mg/kg NMI-amide in mice.

2. Materials and instrument

2.1. Reagents and chemicals

Formic acid and ammonia acetate were purchased from Sigma-Aldrich (St. Louis, MO, USA). Acetonitrile and methanol were obtained from EMD (Billerica, MA, USA). MHI-148 and NMI-amide were synthesized as described [7,9]. Deionized water was prepared using a Barnstead Nanopure Diamond™ water purification system (APS Water Services Corporation, Van Nuys, CA, USA). C57BL6 mouse plasma was purchased from Innovative Research (Novi, MI, USA). C57B/L mice were purchased from Harlan Laboratories (Placentia, CA, USA). The animal studies were performed in accordance with the Guidelines for the Care and Use of Laboratory Animals with protocols approved by the Institutional Animal Care and Use Committee (IACUC) of University of Southern California (Los Angeles, CA, USA).

2.2. HPLC–MS/MS system

The HPLC–MS/MS system consisted of an API 3200 LC-MS/MS system (Sciex, Framingham, MA, USA) and two Shimadzu LC-20AD Prominence liquid chromatograph pumps equipped with an SIL-20A Prominence autosampler (Shimadzu, Columbia, MD, USA). Chromatography separation was carried out using a Symmetry® C_{18} column (4.6 mm × 75 mm, 3.5 μm; Waters, Milford, MA, USA).

The chromatographic separation was carried out using a mobile phase containing 80% acetonitrile and 20% buffer (0.1% formic acid containing 2 mM ammonium acetate) with a flow rate of 1 mL/min. The entire running time was 2.5 min. The temperatures of analytical column and autosampler were both set at room temperature (24 °C).

All the liquid chromatographic eluent was then introduced into the ESI source in the positive ionization mode. The initial 0.5 min eluent was bypassed from the system to avoid unnecessary contamination from the inorganic salts presented in the plasma samples. The mass spectrometric conditions were as follows: gas 1, nitrogen (40 psi); gas 2, nitrogen (40 psi); ion spray voltage, 4500 V; ion source temperature, 400 °C; curtain gas, nitrogen (25 psi). Multiple reaction monitoring (MRM) scanning mode was used to monitor the transition of m/z 491.2–361.9 and m/z 685.3–258.2 for NMI-amide and MHI-148, respectively. The MS conditions for NMI-amide and MHI-148 (Internal standard, IS) are shown in Table 1.

2.3. Sample preparation

The stock solution of NMI-amide and MHI-148 were prepared by dissolving appropriate amount of the standards in methanol to generate a concentration of 1 mg/mL. The stock solution of NMI-amide was further diluted appropriately to generate working solutions with concentrations of 0.05, 0.1, 0.2, 0.5, 1, 2, 5, 10, and 20 μg/mL. The stock solution of MHI-148 was diluted to 0.5 μg/mL using 50% methanol as the IS working solution.

The standard calibration samples were prepared by spiking 10 μL of NMI-amide working solutions and 10 μL of IS working solution into 100 μL of mice plasma to obtain the final nominal concentrations of 0.005, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1, and 2 μg/mL. The solution was vortex-mixed and 300 μL acetonitrile was added. The mixture was mixed vigorously for 1 min, followed by centrifuging at 10,000 g for 5 min. The supernatant was transferred to a sample vial and 10 μL was injected to the HPLC–MS/MS system for analysis. Of these standards, 0.01, 0.1, and 1 μg/mL were used as low, medium, and high quality control (QC) samples, while the others were used as the standard samples for constructing the standard curve.

Table 1
MS conditions for MHI148-clorgyline amide and MHI-148.

Compounds	Precursor ion (m/z)	Product ion (m/z)	DP (V)	EP (V)	CEP (V)	CE (V)	CXP (V)
MHI148-clorgyline amide	491.2 [M+2H]$^+$	361.9	45.0	7.0	24.0	27.0	4.0
MHI-148	685.3 [M+H]$^+$	258.2	101.0	7.5	24.0	85.0	4.0

DP, declustering potential; EP, entrance potential; CEP, collision cell entrance potential; CE, collision energy; CXP, collision cell exit potential.

2.4. Method validation

The validity of the assay method was assessed in terms of linearity, sensitivity, precision, accuracy, recovery, dilution integrity and stability. The QC samples at three concentration levels of low, medium and high concentrations (LQC, MQC and HQC, respectively) as well as sample of lower limit of quantification (LLOQ) were utilized and analyzed for method validation [10–12].

2.4.1. Selectivity and specificity

The selectivity of this method was evaluated by injecting the blank plasma sample or spiked with clorgyline (an MAOA inhibitor usually used as antidepressant) and NMI-amide. Clorgyline was detected using MRM by monitoring the m/z transition of 272.9–82.1 in positive ion mode.

The highest response product ion from the fragmentation of the precursor ion of NMI-amide (491.2) was used as a quantifier, while the next highest product ion (410.5) was used as a qualifier. Monitoring the signals of m/z transition for qualifier ions can confirm the presence of NMI-amide. The quantifier and qualifier signal ratio was determined at LLOQ, LQC, MQC, and HQC levels ($n = 3$). A tolerance of 30% was set for the confirmation as per SANCO/12571/2013 guideline [13].

2.4.2. Linearity and sensitivity

For construction of the standard calibration curve, standard samples were injected in triplicates at concentrations of 0.005, 0.02, 0.05, 0.2, 0.5, and 2 µg/mL. Calibration curve was constructed using the analyte/IS peak area ratio versus the analyte's nominal concentration, and fitted by linear least-squares regression analysis with a weighting factor of $1/x^2$ (x is the value of the nominal concentration).

Sensitivity of the method was evaluated in terms of limit of detection (LOD) and LLOQ. LOD was defined as the concentration of NMI-amide which yields a signal to noise ratio greater than 3. LLOQ was determined based on the two criteria: (1) the analyte response at the LLOQ would be at least 5 times that of the blank; and (2) the analyte peak would be identifiable, discrete, and reproducible with a precision within 20% and accuracy of 80%–120% [10,11].

2.4.3. Precision and accuracy

The intra- and inter-day precisions and accuracy of the method were evaluated using the spiked standard plasma samples at concentrations of LLOQ, 0.01, 0.1 and 1 µg/mL. Precision was calculated as the relative standard deviation (RSD) of the triplicate (inter-day) or five replicates (intra-day) samples, whereas accuracy was assessed as the percentage to the nominal concentration (%). The precision acceptance criteria were set at < 20% for samples at LLOQ concentration, and 15% for other QC samples [10,11].

2.4.4. Recovery

Extraction recovery of NMI-amide and MHI-148 were assessed by comparing the peak areas of the extracted QC samples to the un-extracted standard solutions containing equivalent amount of the analytes. Briefly, 300 µL of acetonitrile was added to 100 µL of blank plasma and the mixture was vortex-mixed for 1 min. Afterwards, 10 µL of NMI-amide working solutions was spiked to final concentrations of 0.01 and 1 µg/mL and MHI-148 working solutions were added. The samples were mixed well as post-extracted QC samples. After centrifuging at 10,000 g for 5 min, the supernatant was removed and analyzed. The peak area, representing 100% recovery, was compared with that from the extracted QC samples.

2.4.5. Dilution integrity

The plasma concentrations for the first few time points following intravenous administration are usually very high (greater than upper limit of quantification limit, ULOQ) and sample dilution is required. Dilution integrity of NMI-amide in plasma was verified by diluting the samples above ULOQ. In this study, five replicates of plasma samples spiked at concentration of 200 µg/mL underwent 100 and 200-fold dilutions to final concentrations of 2 and 1 µg/mL. The diluted samples were then processed and analyzed using the same procedure mentioned in Section 2.3 ($n = 5$). The precision and accuracy were then determined.

2.4.6. Stability

The stability of NMI-amide in terms of storage stability, freeze/thaw stability, injector stability, and handling stability was evaluated during the sample collection and handling, after long-term and short-term storage, freeze-thaw cycles, and after the entire analysis procedure. For storage stability, the QC samples were prepared and stored at −80 °C for 2 weeks. The samples were then processed and analyzed together with the freshly prepared samples. For freeze–thaw stability assessment, QC samples were exposed to three freeze (−80 °C) and thaw on ice for three cycles and then analyzed along with the freshly prepared samples. For injector stability, the prepared samples in the autosampler were evaluated by re-analyzing the samples after being placed at 4 °C for up to 4 h. For the stability during the handling process, the QC samples were prepared and kept on ice for 4 h and then analyzed along with the freshly prepared samples. All these stability tests were performed on two QC concentrations with triplicate samples. The percent deviation in concentration was used as an indicator of stability. The analyte can be considered stable when the percent deviation was within ± 15% of the nominal concentration [10,11].

2.5. Application to pharmacokinetic study

The validated assay method was applied to a pharmacokinetic study of NMI-amide in C57B/L mice following intravenous injection at a dose of 5 mg/kg. Five milligrams NMI-amide was precisely weighed and dissolved in DMSO to yield a concentration of 50 mg/mL and further diluted to 5 mg/mL using 50% glycerol:50% ethanol (1:1, v/v). For intravenous injection, approximate 30 µL of NMI-amide solution was injected via tail vein. Mice were euthanized and blood samples were collected via heart puncture at 0, 2, 5, 15, 30, 60 and 90 min post injection. Three mice were used at each point.

Blood samples were placed on ice immediately and centrifuged at 10,000 g for 3 min at 4 °C. The supernatant plasma was separated and stored at −80 °C until analysis. The plasma samples were then processed and analyzed by the validated HPLC–MS/MS method as described above. Concentration-time profile was constructed and relevant pharmacokinetic parameters were calculated.

3. Results

3.1. Mass spectrometry and chromatography

The MHI dye imaging agent and its derivative were detected using mass spectrometry. The full Q1 scans of NMI-amide and MHI 148 were acquired in positive ion mode by infusing the standard solutions at concentration of 1 µg/mL into the ESI source. The two proton adduct and one proton adduct were found to be the most
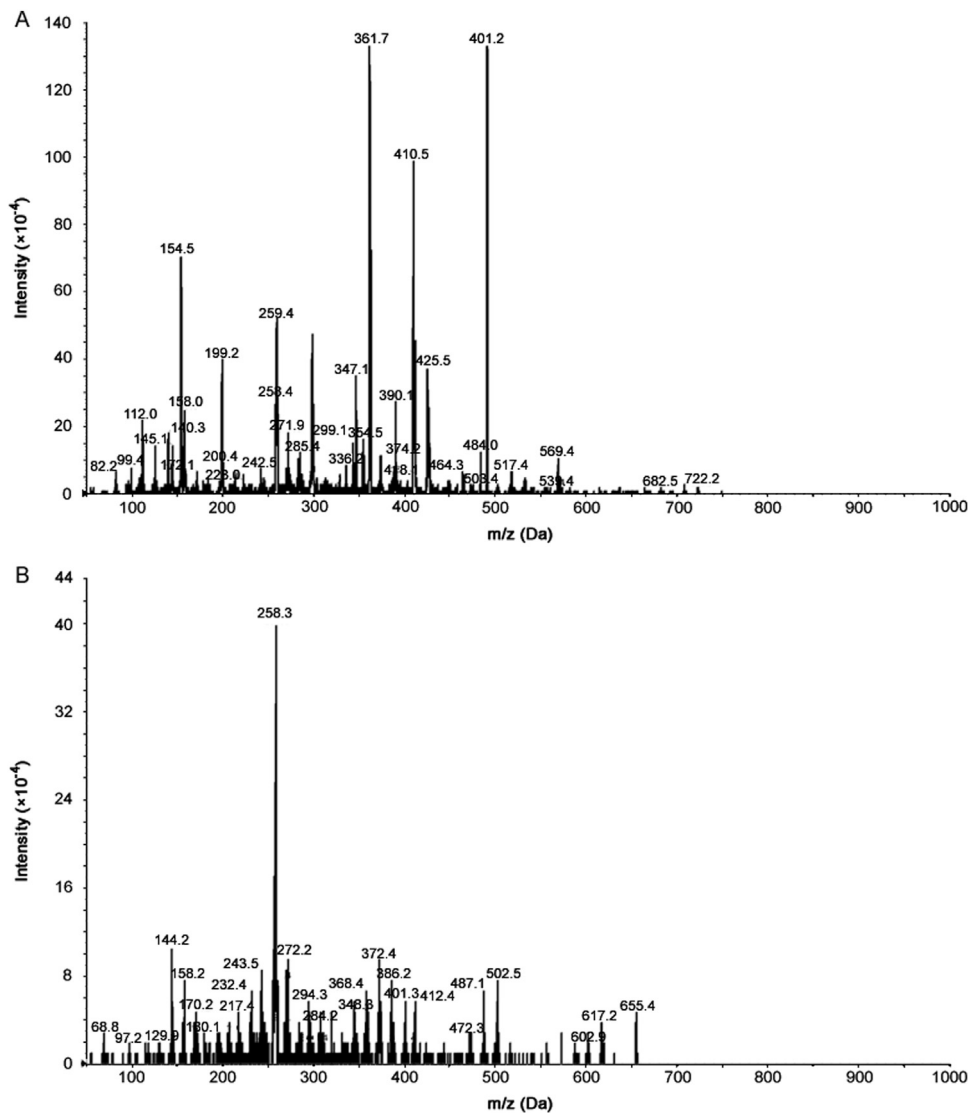
Fig. 2. Product ion mass spectra of (A) NMI-amide and (B) MHI-148 (IS).

intensive ions for NMI-amide (m/z 491.2) and MHI-148 (m/z 685.3), respectively. The product ion mass spectra of these two compounds are shown in Fig. 2. The most abundant product ion of each analyte was selected from MRM monitoring, and the MS/MS conditions were optimized to maximize the response of each of precursor/product transition (Table 1).

3.2. Method validation

3.2.1. Selectivity and specificity

No obvious peak was detected in blank plasma processed with the procedure in Section 2.3. In addition, in the sample spiked with clorgyline, only clorgyline peak was detected at retention time of 0.75 min (Fig. 3A) while NMI-amide was detected without any interference (Fig. 3B).

The ratios of the qualifier peaks to that of the quantifier peaks were (67.5 ± 9.4)%, (73.1 ± 3.3)%, (72.5 ± 2.0)% and (71.2% ± 1.4)% for LLOQ, LQC, MQC, and HQC, respectively. The RSD values were less than 13.9% (Fig. 4), indicating good specificity.

3.2.2. Linearity and sensitivity

The calibration curve of NMI-amide was linear over the concentration range of 0.005–2 µg/mL with the regression coefficient

greater than 0.99, which is acceptable according to the FDA guidelines [10].

The standard curves are expressed as $y = ax + b$, where x is the concentration and y is the ratio of the signal intensity of test compounds over internal standard. The parameters of a and b are the corresponding slop and intercept, respectively. The following relationship was obtained: $y = 0.1337x + 0.1028$.

The representative MRM chromatograms of the QC sample at concentration of 1 µg/mL, IS (50 ng/mL) and a real plasma sample at 1 h post dose administration (the concentration was calculated to be 0.59 µg/mL) are shown in Figs. 3 C–G. No specific interference was observed surrounding the NMI-amide or IS peak. The LOD and LLOQ were found to be 0.0025 and 0.005 µg/mL, respectively.

3.2.3. Accuracy and precision

The precision and accuracy of the assay method for NMI-amide are summarized in Table 2. For QC samples at concentrations of LLOQ, 0.01, 0.1, and 1 µg/mL, the intra- and inter-day precisions (RSD) ranged from 1.1% to 14.0%. The accuracy, presented as percent deviation from the nominal concentrations, ranged from
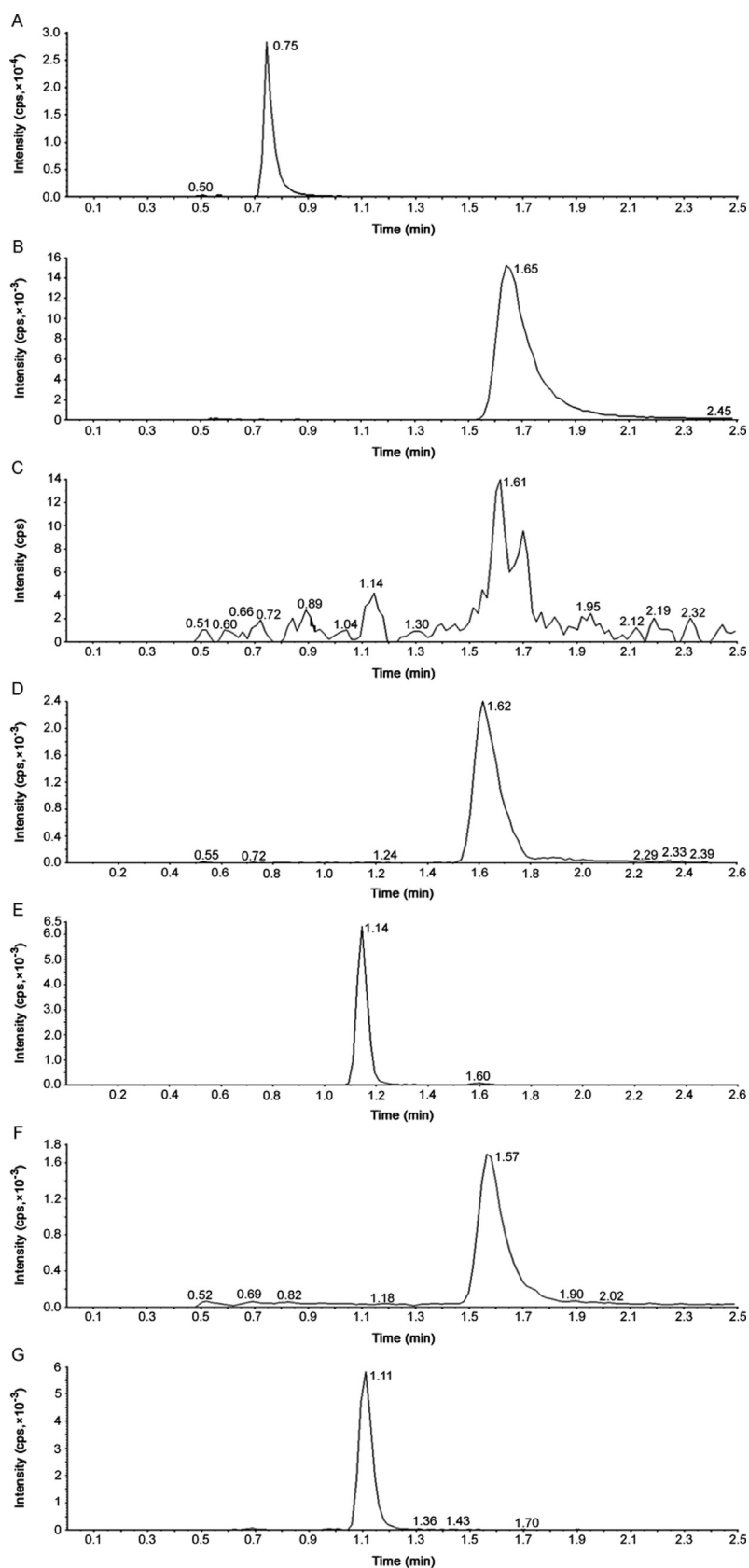
Fig. 3. MRM chromatograms of (A, B) clorgyline and NMI-amide from plasma sample spiked with clorgyline and NMI-amide, respectively; (C) blank plasma, (D) NMI-amide (1 μg/mL), (E) MHI-148, (IS, 50 ng/mL) and (F, G) NMI-amide and IS of a plasma sample of 1 h post dose administration.

86.8% to 113.2%. These results indicated that this method was accurate, precise and reproducible for quantification of NMI-amide in mouse plasma.

3.2.4. Recovery

The protein precipitation extraction method yielded a recovery of 85.4% and 95.9% for NMI-amide at LQC and HQC, respectively,
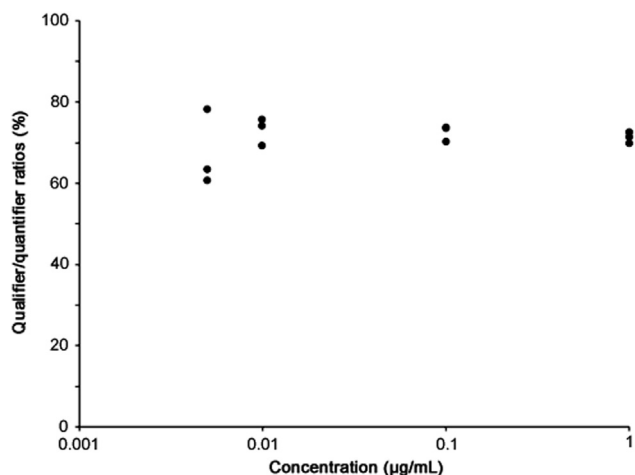
Fig. 4. Qualifier/quantifier peak ratios for samples at LLOQ, LQC, MQC, and HQC levels. (Quantifier: 491.2–361.9; Qualifier: 491.2–410.5).

Table 2
Precision and accuracy for MHI148-clorgyline amide analysis.

Nominal concentration (μg/mL)	Intra-day		Inter-day	
	Accuracy (%)	Precision (%)	Accuracy (%)	Precision (%)
0.005	107.6	9.8	104.4	2.8
0.01	86.8	7.0	99.3	14.0
0.1	104.2	1.1	106.0	11.6
1	113.2	8.6	109.4	6.6

Table 3
Recovery of MHI148-clorgyline amide and MHI-148.

Analyte	Conc. (μg/mL)	Recovery (%)
MHI148-clorgyline amide	0.01	85.4 ± 19.9
	1	95.9 ± 9.1
MHI-148 (IS)	0.05	59.7 ± 10.7

and 59.7% for the IS (MHI-148, Table 3), which suggested that recovery rates were consistent over the calibration ranges. Although the recovery of the IS was relatively low compared to that of NMI-amide, it did not affect the assay precision or accuracy. Thus, no further improvement of its recovery was attempted.

3.2.5. Dilution integrity

The original concentrations of the samples being diluted were back calculated. The accuracy values were 86.4% and 92.8% for 100- and 200-fold dilutions, respectively, while the precision was within 9.9% for both dilutions. The samples of the first three time points (2, 5, and 15 min) underwent dilution before assay.

3.2.6. Stability

NMI-amide was found stable under the storage condition (−80 °C) for at least two weeks and at least 4 h on ice (4 °C). In our preliminary study, NMI-amide was found unstable in plasma at room temperature with a degradation half-life of 11 h and 22 h for low concentration and high concentration, respectively. Thus, all the stock solutions and plasma samples were placed on ice during the entire process. The duration of sample preparation was kept within 4 h. The stability test results showed that NMI-amide was stable under current experiment settings (Table 4).

Table 4
Stability of MHI148-clorgyline amide under different conditions.

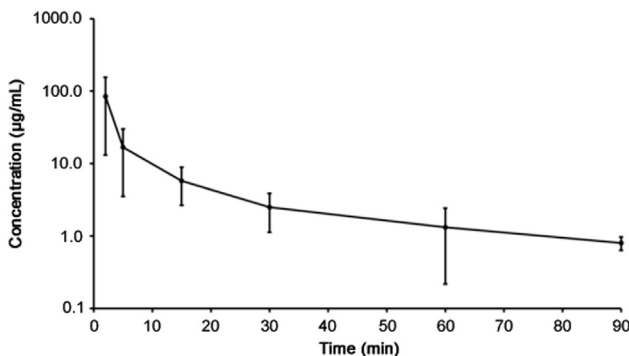| Condition	Conc. (μg/mL)	Measured conc. (μg/mL)
Handling stability (4 h on ice)	0.01	0.0099 ± 0.0005
	1	0.94 ± 0.10
Freeze and thaw stability (3 freeze (−80 °C) and thaw (on ice) cycles)	0.01	0.0095 ± 0.0009
	1	0.95 ± 0.03
Injector stability (4 h in the autosampler)	0.01	0.0098 ± 0.0010
	1	1.00 ± 0.09
Storage stability (2 weeks at −80 °C)	0.01	0.010 ± 0.004
	1	1.05 ± 0.06

Fig. 5. Plasma concentration-time profile of NMI-amide in mice after an intravenous dose of 5 mg/kg.

3.3. Pharmacokinetic results

The mean plasma concentration–time profile of NMI-amide in C57B/L mice following intravenous injection at a dose of 5 mg/kg is shown in Fig. 5. The pharmacokinetic profile after intravenous injection indicates that NMI-amide pharmacokinetics followed a typical three-compartmental model with a very rapid distribution phase and a slow terminal elimination phase ($t_{1/2}$ of 36.6 min). All other relevant pharmacokinetic parameters are listed in Table 5.

4. Discussion

MHI dye imaging agent was for the first time detected and quantified using an HPLC and mass spectrometry based method. Such method could provide much higher sensitivity which is necessary for pharmacokinetic studies. Before developing the HPLC–MS/MS method, a UV detector was used with the maximum absorption wavelength of NMI-amide at 400 nm. However, the sensitivity of this method was too low and not feasible for a pharmacokinetic study. NMI-amide was well detected using mass spectrometry with acceptable sensitivity (LLOQ 5 ng/mL). The doubly protonated ion $[M + 2H]^{2+}$ was found to be most intensive as the parent ion for NMI-amide with the daughter ion fragments shown in Fig. 2A. Among these daughter ions, the highest response ion (361.7) was selected as a quantifier, while the second highest ion (410.5) as a qualifier. The variation of the peak ratio (qualifier/quantifier) was < 13.9% for all the samples tested, which was within the tolerance (30%) suggested by SANCO/12571/2013 guideline [13]. The results indicated a good specificity of this MS/MS method.

NMI-amide was found temperature sensitive and not stable at room temperature. Thus, the whole process of sample preparation

Table 5
Pharmacokinetic parameters of MHI148-clorgyline amide following an intravenous dose of 5 mg/kg ($n = 3$).

Parameters	Mean value
$t_{1/2}$ (min)	36.6
$AUC_{0-90\ min}$ (μg h/mL)	831.81
AUC_{0-inf} (μg h/mL)	832.76
CL (mL/h/kg)	7.75
V_d (mL/kg)	9.73

(formulation preparation, blood sampling, plasma separation, and compound extraction) was carried out on ice or under 4 °C whenever possible. Under this condition, NMI-amide was identified to be stable at least for 4 h, which could guarantee the completion of the assay without significant degradation of NMI-amide.

The internal standard, MHI-148, can be used as an imaging agent for cancers detection using a fluorescence detector [4,14], while its derivative, NMI-amide, can also be detected by a fluorescence detector or UV detector. However, the mass spectrometry was utilized with higher sensitivity and specificity. The recovery of MHI-148 was relatively low, probably due to the high protein binding. As a type of near infrared heptamethine cyanine dye, MHI-148 may bind to albumin and/or low-density lipoprotein [15]. However, the recovery was found to be stable and had no significant impact on the method reproducibility.

The assay method was found sensitive enough for quantification of NMI-amide in plasma sample up to 1.5 h. The pharmacokinetic profile of NMI-amide indicated that it may follow a three-compartmental model which suggests that the permeability of NMI-amide is quite different in central compartments (main the blood) and tissues. A relative short plasma elimination half-life was observed for NMI-amide (36.6 min) which may be caused by the metabolism and/or chemical degradation. This information will be used for dosage determination for future efficacy study and/or clinical trials.

5. Conclusions

A new HPLC–MS/MS assay for NMI-amide in mouse plasma has been successfully established and validated. This assay method is highly sensitive and specific, which has been proven useful for a pharmacokinetic study. The availability of this validated analytical method for NMI-amide will facilitate its further development as a novel tumor-targeting agent.

Conflicts of interest

Drs. B. Olenyuk and JC Shih have the patent on MHI-clorgyline, which is the same compound as MHI148-clorgylineamide (NMI-amide).

References

[1] J.C. Shih, K. Chen, M.J. Ridd, Monoamine oxidase: from genes to behavior, Annu. Rev. Neurosci. 22 (1999) 197–217.
[2] M. Bortolato, K. Chen, J.C. Shih, Monoamine oxidase inactivation: from pathophysiology to therapeutics, Adv. Drug Deliv. Rev. 60 (2008) 1527–1533.
[3] V. Flamand, H. Zhao, D.M. Peehl, Targeting monoamine oxidase A in advanced prostate cancer, J. Cancer Res. Clin. Oncol. 136 (2010) 1761–1771.
[4] J.B. Wu, C. Shao, X. Li, et al., Monoamine oxidase A mediates prostate tumorigenesis and cancer metastasis, J. Clin. Invest. 124 (2014) 2891–2908.
[5] H. Zhao, V. Flamand, D.M. Peehl, Anti-oncogenic and pro-differentiation effects of clorgyline, a monoamine oxidase A inhibitor, on high grade prostate cancer cells, BMC Med. Genom. 2 (2009) 55.
[6] J.B. Wu, T.P. Lin, J.D. Gallagher, et al., Monoamine oxidase A inhibitor–near-infrared dye conjugate reduces prostate tumor growth, J. Am. Chem. Soc. 137 (2015) 2366–2374.
[7] S. Kushal, W. Wang, V.P. Vaikari, et al., Monoamine oxidase A (MAO A) inhibitors decrease glioma progression, Oncotarget 7 (2016) 13842–13853.
[8] J. Logan, J.S. Fowler, Y.S. Ding, et al., Strategy for the formation of parametric images under conditions of low injected radioactivity applied to PET studies with the irreversible monoamine oxidase a tracers [11C]Clorgyline and deuterium-substituted [11C] clorgyline, J. Cereb. Blood Flow Metab. 22 (2002) 1367–1376.
[9] J. Yuan, X. Yi, F. Yan, et al., Near-infrared fluorescence imaging of prostate cancer using heptamethine carbocyanine dyes, Mol. Med. Rep. 11 (2015) 821–828.
[10] US FDA, Guidance for Industry Bioanalytical Method Validation, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Rockville, Maryland, USA, 2001.
[11] European Medicines Agency, Guideline on Bioanalytical Method Validation, 2011.
[12] Z. Wang, S. Qian, Q. Zhang, et al., Quantification of meclizine in human plasma by high performance liquid chromatography-mass spectrometry, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 879 (2011) 95–99.
[13] European Commission, Health & Consumer protection Directorate-General, Guidance document on analytical quality control and validation procedures for pesticide residues analysis in food and feed, SANCO/12571/2013, 2013.
[14] X. Yang, C. Shi, R. Tong, et al., Near IR heptamethine cyanine dye–mediated cancer imaging, Clin. Cancer Res. 16 (2010) 2833–2844.
[15] C. Shi, J.B. Wu, D. Pan, Review on near-infrared heptamethine cyanine dyes as theranostic agents for tumor imaging, targeting, and photodynamic therapy, J. Biomed. Opt. 21 (2016) 50901.