

Investigation of the Inhibitory Effect of Simvastatin on the Metabolism of Lidocaine Both in vitro and in vivo

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Background: Lidocaine has cardiovascular and neurologic toxicity, which is dose-dependent. Due to CYP3A4-involved metabolism, lidocaine may be prone to drug-drug interactions.

Materials and Methods: Given statins have the possibility of combination with lidocaine in the clinic, we established in vitro models to assess the effect of statins on the metabolism of lidocaine. Further pharmacokinetic alterations of lidocaine and its main metabolite, monoethylglycinexylidide in rats influenced by simvastatin, were investigated.

Results: In vitro study revealed that simvastatin, among the statins, had the most significant inhibitory effect on lidocaine metabolism with IC₅₀ of 39.31 μ M, 50 μ M and 15.77 μ M for RLM, HLM and CYP3A4.1, respectively. Consistent with in vitro results, lidocaine concomitantly used with simvastatin in rats was associated with 1.2-fold AUC_(0-t), 1.2-fold AUC_(0-∞), and 20%-decreased clearance for lidocaine, and 1.4-fold C_{max} for MEGX compared with lidocaine alone.

Conclusion: Collectively, these results implied that simvastatin could evidently inhibit the metabolism of lidocaine both in vivo and in vitro. Accordingly, more attention and necessary therapeutic drug monitoring should be paid to patients with the concomitant coadministration of lidocaine and simvastatin so as to avoid unexpected toxicity.

Keywords: lidocaine, simvastatin, drug-drug interaction, pharmacokinetics, in vitro model

Introduction

Lidocaine, an antiarrhythmic drug, is widely used to treat ventricular arrhythmias, especially in patients with acute myocardial infarction or cardiac surgery.¹⁻⁵ Lidocaine is accompanied by serious adverse effects, which are primarily divided into two categories, cardiovascular and neurologic.¹ Compared to cardiovascular toxicity, the occurrence of neurologic toxicity is more frequent and significant, which is dose-dependent.¹ Patients may experience numbness, dizziness and light-headedness even when lidocaine is administered at a therapeutic dose, while seizures, muscular spasms, visual disturbances, hallucinations, confusion and agitation may occur when the lidocaine plasma concentration is above the normal level.^{1,6} Consequently, therapeutic drug monitoring may be recommended when lidocaine is applied in the clinic.

Previous studies have revealed that lidocaine is primarily metabolized by CYP3A4 to form monoethylglycinexylidide (MEGX), whose potency is lower than lidocaine but cardiovascular and neurologic toxicity is parallel to lidocaine.⁷⁻¹⁵

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Because of CYP-based metabolism, lidocaine may be prone to drug–drug interactions, which means its pharmacokinetic and pharmacodynamic response would be altered when co-administrated with CYP3A4 modulators.

In patients with hyperlipemia, the accumulation of fatty in the intima of arteries would increase the risk of coronary atherosclerosis, and the latter is highly associated with ventricular arrhythmias, which indicates patients may take statins (such as simvastatin) and lidocaine simultaneously.^{16–19} It's reported that simvastatin is mainly metabolized by CYP3A4/5 and can inhibit CYP3A activity.²⁰ An in vitro study exhibited that simvastatin could competitively inhibit the metabolism of midazolam (a CYP3A4 substrate) with K_i at 10 μ M, and an in vivo study showed that co-administration with simvastatin resulted in 1.42-fold increment of $AUC_{(0-t)}$ and 1.96-fold prolongation of $t_{1/2}$ for sinomenine (a CYP3A4 substrate).^{20,21} Therefore, there may be a drug–drug interaction between lidocaine and simvastatin.

In this study, we established several in vitro models to assess the effects of other statins on the metabolism of lidocaine compared with that of simvastatin, and further investigated the potential drug–drug interaction between lidocaine and simvastatin in rats. Moreover, the impacts of simvastatin on lidocaine metabolism in rat/human liver microsome and recombinant human CYP3A4.1 microsome were identified.

Materials and Methods

Chemical and Reagents

Lidocaine, simvastatin and bupivacaine (served as internal standard, IS) were purchased from Beijing Sunflower and Technology Development Co., Ltd (Beijing, China) and MEGX was from Toronto Research Chemicals Inc (Toronto, Ontario, Canada). Lidocaine hydrochloride for subcutaneous administration to rats was purchased from Shandong Hualu Pharmaceutical Co., Ltd (Shandong, China). Phosphate buffer saline (PBS) and the reduced nicotinamide adenine dinucleotide phosphate (NADPH) were bought from Beyotime Biotechnology (Shanghai, China) and Roche Pharmaceutical Ltd. (Basel, Switzerland), respectively. Pooled rat/human liver microsome (RLM/HLM) were from Corning Life Sciences Co., Ltd (Wujiang, China), while recombinant human CYP3A4.1 protein and cytochrome b5 were kind gifts from Beijing Hospital (Beijing, China).²² Acetonitrile was purchased from Merck (Darmstadt, Germany) and formic acid was from Sigma-Aldrich Co. (St. Louis, MO, USA), both of which were of analytical grade.

Equipment and Operation Conditions

An Acquity UPLC-MS/MS system (Waters Corp., Milford, MA, USA) was employed for the isolation of lidocaine, MEGX and bupivacaine. These analytes were chromatographed on an Acquity BEH C18 column (2.1 mm×50 mm, 1.7 μ m) at 40°C using a mobile phase consisting of acetonitrile and water (0.1% formic acid) with a gradient elution program at a flow rate of 0.4 mL/min (Table 1). The multiple-reaction-monitoring (MRM) transitions in a positive mode were used to quantify these analytes and their corresponding monitored transitions and parameters are displayed in Table 2.

In vitro Kinetic Parameters for Lidocaine in RLM/HLM

The in vitro models selected in our study included RLM and HLM. The 200- μ L RLM/HLM incubation system consisted of lidocaine, 0.5mg/mL RLM or 0.2mg/mL HLM, 100 mmol PBS (pH 7.4) and 1 mM NADPH. To confirm the K_m value, the concentrations of lidocaine were designed at 10–1000 μ M for RLM and 100–3000 μ M for HLM. After 5-min preincubation at 37°C, 1 mM NADPH was added to initiate the reaction. After 40-min incubation,

Table 1 The Developed Gradient Elution Program for the Isolation of Lidocaine, Monoethylglycinexylidide (MEGX) and Bupivacaine

Time (min)	Flow Rate (mL/min)	Mobile Phase	
		Water (0.1% Formic acid)	Acetonitrile
0	0.4	90%	10%
0.5	0.4	90%	10%
1.0	0.4	10%	90%
2.0	0.4	10%	90%
2.1	0.4	90%	10%
3.0	0.4	90%	10%

Table 2 Mass-to-Charge (m/z) Values for the Protonated Lidocaine, Monoethylglycinexylidide (MEGX) and Bupivacaine Obtained by ESI+ and Mass Transitions Used for Quantification in the Multiple-Reaction-Monitoring Mode

Analytes	Mass Transition (m/z to m/z)	Cone Voltage (V)	Collision Energy (V)
Lidocaine	235→86	25	27
MEGX	207.2→58	30	10
Bupivacaine	289.11→140.41	25	20

the incubation system was frozen at -80°C to stop the reaction. After the addition of $400\mu\text{L}$ of acetonitrile and $20\mu\text{L}$ of bupivacaine ($50\mu\text{g}/\text{mL}$), the incubation system was suffered from 2-min vortex and 10-min centrifugation at 13,000 rpm, and a $20\mu\text{L}$ aliquot of the supernatant was diluted with 1 mL ultra-pure water then for UPLC-MS/MS analysis. All samples were performed in triplicate.

Comparison of Inhibitory Effects Between Simvastatin and Other Statins in RLM/HLM

The in vitro models selected in our study included RLM and HLM. The $200\text{-}\mu\text{L}$ incubation system contained lidocaine ($250\text{ }\mu\text{M}$ for RLM and $1000\text{ }\mu\text{M}$ for HLM, based on their own K_m values), RLM ($0.5\text{mg}/\text{mL}$) or HLM ($0.2\text{mg}/\text{mL}$), and 1 mM NADPH in 100 mmol PBS (pH 7.4) with/without the presence of statins ($100\mu\text{M}$). The following processing steps were the same as the above experiments.

Inhibitory Effect of Simvastatin on Lidocaine in RLM, HLM and CYP3A4.1

The in vitro models selected in our study included RLM, HLM and recombinant CYP3A4 enzyme. The CYP3A4.1 incubation system referred to our previous study.²³ The $200\text{-}\mu\text{L}$ incubation system contained lidocaine ($250\text{ }\mu\text{M}$ for RLM, $1000\text{ }\mu\text{M}$ for HLM and $500\text{ }\mu\text{M}$ for CYP3A4.1, based on their own K_m values), RLM ($0.5\text{mg}/\text{mL}$) or HLM ($0.2\text{mg}/\text{mL}$) or CYP3A4.1 (5pmol) coupled with b5 (5pmol), and 1 mM NADPH in 100 mmol PBS (pH 7.4) with the presence of simvastatin (0, 0.01, 0.1, 1, 10, 25, 50 and $100\mu\text{M}$). The following processing steps were the same as the above experiments.

Inhibitory Effect of Simvastatin on Lidocaine in Rats

Male Sprague–Dawley rats (180–200 g) were obtained from Shanghai Laboratory Animal Center and maintained in the Laboratory Animal Center of Wenzhou Medical University in a temperature-controlled environment with a 12 h light-dark cycle. Animals had free access to standard laboratory food and tap water. All experiments were performed after the approval of the Animal Care and Use Committee of Wenzhou Medical University (Wenzhou, China, License No. WYDW [ZJ] 2019–0002) and followed the Guide for the Care and Use of Laboratory Animal.

Before the experiments, rats were fasted for 12 h but free to water. $8\text{ mg}/\text{mL}$ lidocaine hydrochloride was diluted by $20\text{ mg}/$

mL lidocaine hydrochloride with normal saline. Simvastatin was dissolved in 0.5% Carboxymethylcellulose sodium salt solution to achieve a concentration at $20\text{ mg}/\text{mL}$. Twelve rats were randomly divided into two groups ($n=6$): control group (group A, lidocaine alone) and study group (group B, lidocaine and simvastatin). $40\text{ mg}/\text{kg}$ simvastatin was orally pretreated to group B and an equivalent volume of 0.5% CMC-Na solution was orally pretreated to group A. 30 minutes later, $10\text{ mg}/\text{kg}$ lidocaine was administrated subcutaneously to the two groups. Simvastatin has been reported to have an inhibitory effect on CYP3A4 and lidocaine has been identified as a substrate of CYP3A4, which means simvastatin may be a mechanism-based inhibitor for lidocaine. Therefore, it is recommended that the administration of simvastatin was half an hour earlier than that of lidocaine to maximize the effect of the potential interaction.^{24–28} Subsequently, the blood samples (ca. 0.3 mL) were collected from the tail vein into tubes containing sodium heparin at 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h after the administration of lidocaine. The collected sample was processed by centrifugation ($13,000\text{ rpm}$ for 10 min), the $100\text{-}\mu\text{L}$ plasma was mixed with $20\mu\text{L}$ of bupivacaine ($100\text{ ng}/\text{mL}$) and $400\mu\text{L}$ of acetonitrile, the mixture was stirred for 2 min and centrifuged at $13,000\text{ rpm}$ for 15 min, and a $50\mu\text{L}$ aliquot of the supernatant was diluted with $200\mu\text{L}$ of ultra-pure water then for UPLC-MS/MS analysis.

Statistical Analysis

The in vitro kinetic parameters and the IC_{50} values were calculated with GraphPad Prism 5.0 (Graphpad Software Inc., San Diego, CA, USA) by Michaelis-Menten analysis and $\log(\text{inhibitor})$ vs normalized response analysis, respectively. Pharmacokinetic profiles in rats were analyzed by noncompartmental methods using DAS software (Version 3.0, Bontz Inc., Beijing, China) and the concentration–time curves were depicted using Origin 8.0 (Originlab Company, Northampton, MA, USA). The main pharmacokinetic profiles between group A and group B were statistically analyzed by unpaired t -test analysis using GraphPad Prism 5.0. $P<0.05$ meant statistical significance.

Results

UPLC-MS/MS

The representative chromatograms of lidocaine, MEGX and bupivacaine in blank plasma (A), blank plasma spiked with analytes (B), and plasma at 2 h after the administration of lidocaine (C) are displayed in Figure 1. Although some interfering peaks are observed at the elution time of the

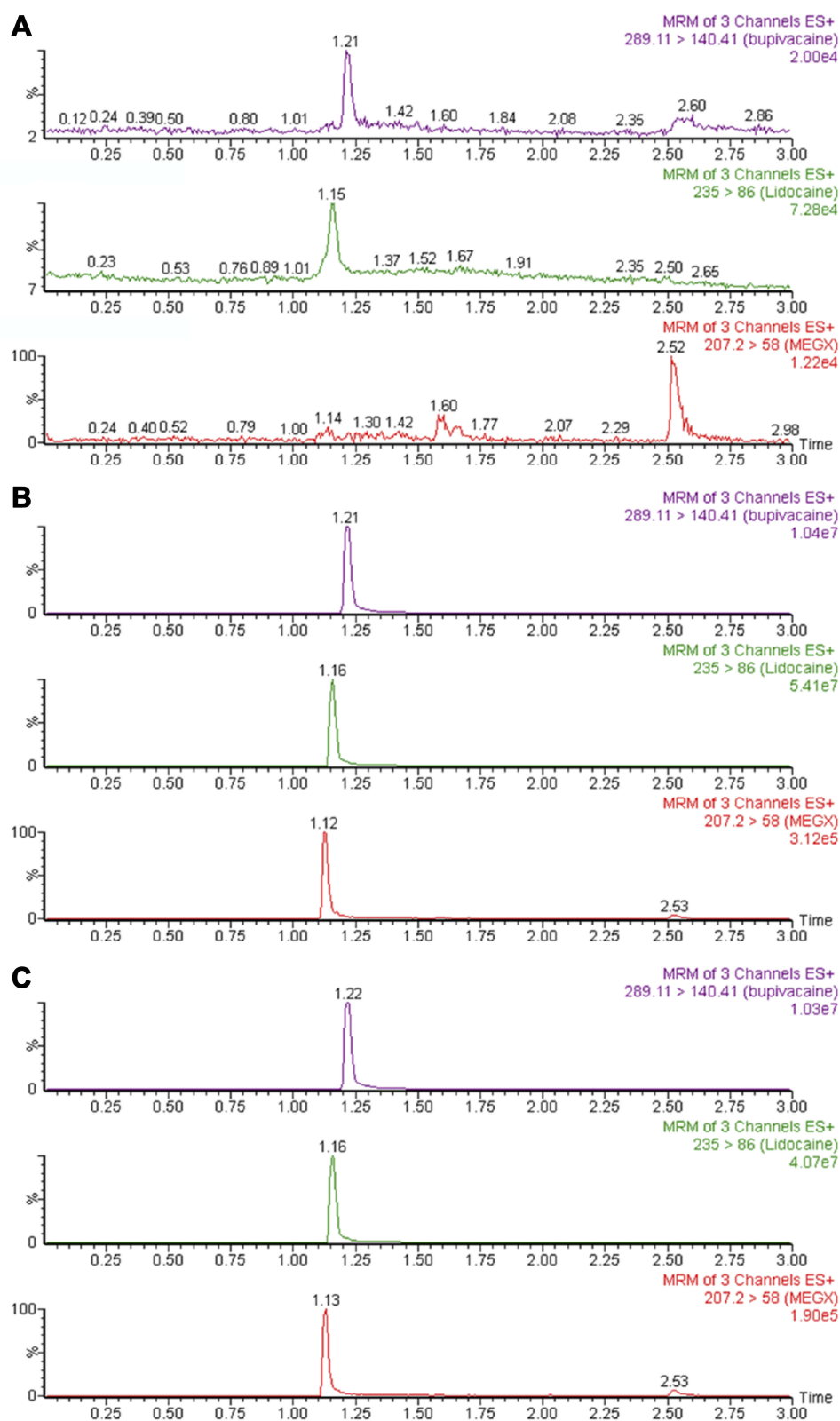


Figure 1 UPLC-MS/MS chromatographs of lidocaine, monoethylglycinexylidide (MEGX) and bupivacaine. **(A)** Blank plasma sample. **(B)** Blank plasma spiked with 200 ng/mL lidocaine, 0.5 ng/mL MEGX and 100 ng/mL bupivacaine. **(C)** Simvastatin-treated rat plasma sample at 2 h after the administration of lidocaine.

two analytes and bupivacaine in a blank plasma sample, their responses were less than 20% of the responses of the LLOQ sample for lidocaine and MEGX, and 5% for bupivacaine. Bupivacaine did not affect the measurement of the two analytes. Additionally, there was no carry-over effect. The concentrations of calibration curves were set at 10–2000 ng/mL for lidocaine and 0.1–50 ng/mL for MEGX, respectively. The concentrations of quality control samples were set at 10, 20, 800 and 1600 ng/mL for lidocaine, and 0.1, 0.2, 20 and 40 ng/mL for MEGX, respectively, all of which were validated according to FDA and EMEA guidelines for bioanalytical validation.^{29,30} They were within the acceptable limits and their corresponding data about accuracy, precision, recovery, matrix effect and stability are presented in [supplementary Tables 1–3](#).

In vitro Kinetic Parameters for Lidocaine in RLM/HLM

In RLM, the Michaelis-Menten curve of lidocaine is plotted in [Figure 2\(A\)](#) and its kinetic parameters were calculated, in which V_{\max} value was 8.858 ± 0.037 nmol/min/mg and K_m value was 216.750 ± 1.344 μ M. In HLM, the Michaelis-Menten curve is depicted in [Figure 2\(B\)](#), and V_{\max} and K_m values were calculated at 5.21 ± 0.04 nmol/min/mg and 1027.50 ± 16.26 μ M, respectively.

Effects of Simvastatin and Other Statins on the Metabolism of Lidocaine in vitro

The results of the comparison of inhibitory effects on lidocaine between simvastatin and other statins (lovastatin, rosuvastatin and atorvastatin) are exhibited in [Figure 3](#).

Simvastatin inhibited the metabolism of lidocaine to 21.97% in RLM and 16.58% in HLM, while lovastatin, rosuvastatin and atorvastatin inhibited to 54.42%, 93.91% and 89.74% in RLM, and 56.05%, 96.33% and 97.96% in HLM, respectively. These results manifested that the inhibition by simvastatin was most significant and the outcomes in RLM and HLM were consistent, indicating the combination of lidocaine and simvastatin might have a high likelihood of drug–drug interaction.

The IC_{50} curves of simvastatin on the metabolism of lidocaine in RLM, HLM and CYP3A4.1 are displayed in [Figure 4](#) and the corresponding IC_{50} values were 39.31 μ M, 50 μ M, and 15.77 μ M, respectively. When the concentration of simvastatin was 100 μ M, lidocaine metabolism was inhibited by 78.03%, 83.42% and 74% in RLM, HLM and CYP3A4.1, respectively.

Effects of Simvastatin on the Metabolism of Lidocaine in vivo

The concentration–time curves of lidocaine and MEGX are shown in [Figure 5](#) and their corresponding pharmacokinetic parameters were shown in [Tables 3](#) and [4](#). In comparison with the control group, lidocaine exposure in the study group was enhanced with 1.2-fold $AUC_{(0-t)}$ ($P < 0.05$) and 1.2-fold $AUC_{(0-\infty)}$ ($P < 0.05$), and its clearance was decreased with $CL_{Z/F}$ value from 4.143 ± 0.715 L/h/kg to 3.370 ± 0.419 L/h/kg ($P < 0.05$). MEGX exposure was also increased with C_{\max} value from 25.032 ± 6.101 ng/mL to 33.799 ± 6.788 ng/mL, approximately 1.4-fold increment. Besides, there is no significant difference among other pharmacokinetic parameters between the control group and the study group ($P > 0.05$).

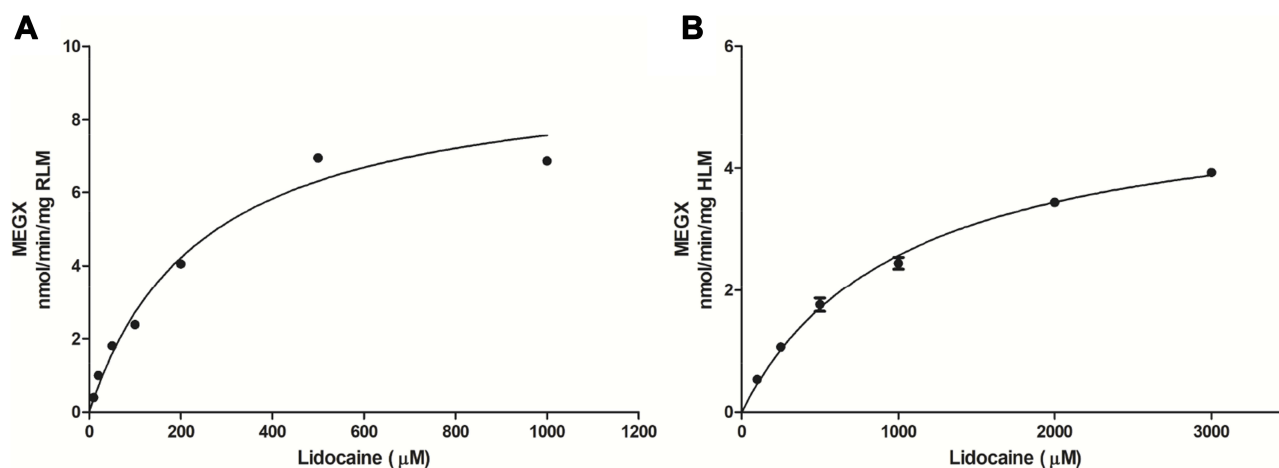


Figure 2 Michaelis-Menten curves for lidocaine in rat liver microsome (RLM), (A) and human liver microsome (HLM). (B) Values are the mean \pm SD, N=3.

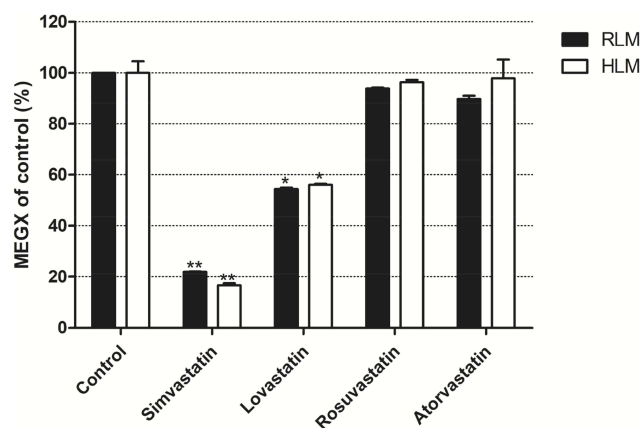


Figure 3 Inhibitory comparison of statins on the metabolism of lidocaine in rat liver microsomes (RLM) and human liver microsomes (HLM). Values are the mean \pm SD, N=3.

Notes: Significant difference between statins and the control was analyzed by one-way ANOVA with Dunnett's test. * $P < 0.05$, ** $P < 0.01$

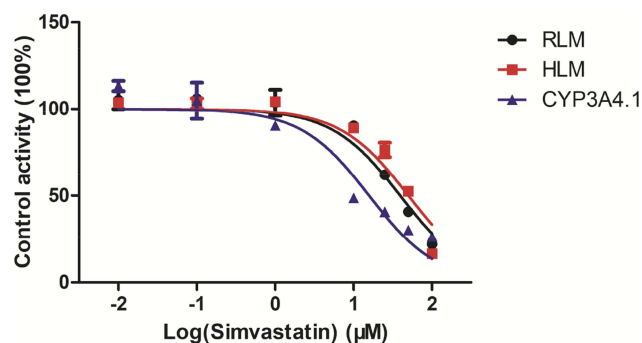


Figure 4 Simvastatin with various concentrations on the metabolism of lidocaine for half-maximal inhibitory concentration (IC_{50}) in the activity of RLM, HLM and CYP3A4.1. Values are the mean \pm SD, N=3.

Discussion

The clinical use of lidocaine may result in cardiotoxicity and neurotoxicity, and the latter is related to dose, which implies the higher lidocaine plasma concentration would be more likely to induce neurotoxicity.^{1,6} As the involvement of CYP3A4, the metabolism of lidocaine is susceptible to other drugs, with a high risk of potential interactions and adverse reactions.

Several in vitro models are usually employed for metabolic researches, including liver slices, liver microsomes, hepatocyte and recombinant enzyme.^{31,32} It is higher-throughput, more rapid and sensitive with less interference factors compared with in vivo models.²¹ Accordingly, we established RLM and HLM incubation systems to obtain the in vitro kinetic parameters for lidocaine and to study the combination of lidocaine with statins that may be co-administrated with lidocaine in the clinic. The in vitro results showed that simvastatin could significantly inhibit lidocaine metabolism with IC_{50} of 39.31 μ M in RLM, which underlay the potential interaction between lidocaine and simvastatin in rats. The IC_{50} value of 50 μ M in HLM meant the results obtained in rats might be extrapolated to human to some extent. Further inhibition in CYP3A4.1 with IC_{50} of 15.77 μ M elucidated lidocaine metabolism inhibited by simvastatin was mainly via CYP3A4.

Consistent with in vitro results, the metabolism of lidocaine inhibited by simvastatin also occurred in rats. Lidocaine plasma concentrations were obviously increased and the clearance was evidently decreased, which may be explained by the inhibition of CYP3A4 activity. It is reported

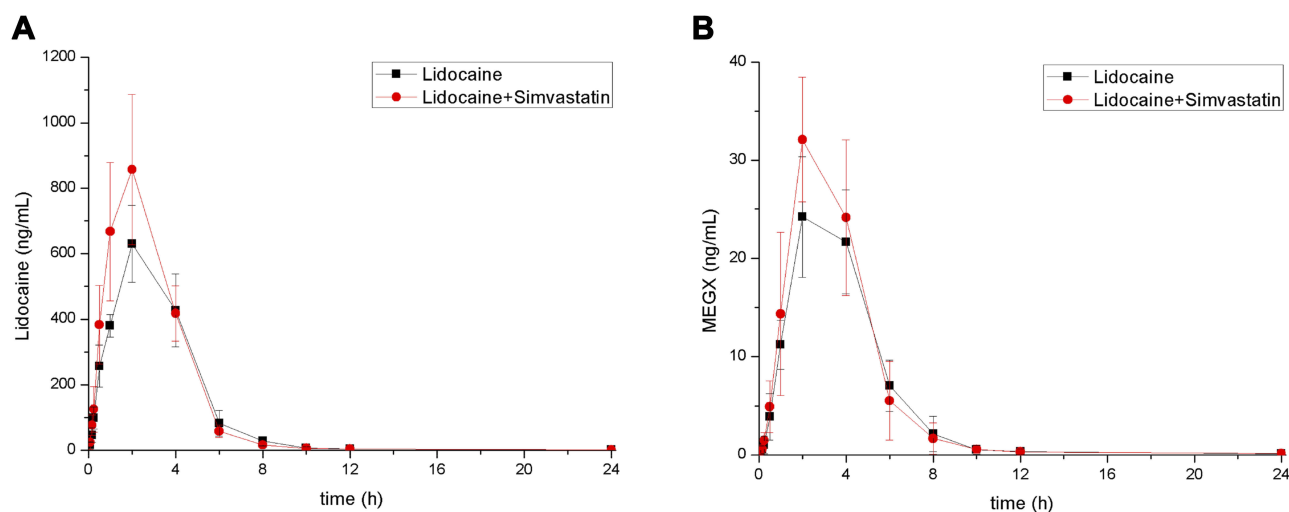


Figure 5 Mean concentration–time curves of lidocaine (A) and monoethylglycinexylidide (MEGX), (B) in the control group (lidocaine alone) and the study group (lidocaine with simvastatin). Values are the mean \pm SD, N=6.

Table 3 The Main Pharmacokinetic Parameters of Lidocaine in Two Groups of Rats (N=6)

Parameters	Unit	Control Group	Study Group
AUC _(0-t)	μg/L×h	2475.589 ± 435.909	2999.597 ± 371.492*
AUC _(0-∞)	μg/L×h	2476.355 ± 436.898	3006.558 ± 375.827*
C _{max}	μg/L	629.676 ± 116.966	857.747 ± 229.825
T _{max}	h	2.000 ± 0.000	2.000 ± 0.000
t _{1/2z}	h	1.764 ± 0.747	3.664 ± 4.019
V _{z/F}	L/kg	10.287 ± 3.363	17.026 ± 17.685
CL _{z/F}	L/h/kg	4.143 ± 0.715	3.370 ± 0.419*

Note: *P<0.05 in comparison with the control group.

Abbreviations: AUC, area under the blood concentration–time curve; C_{max}, maximum blood concentration; T_{max}, peak time; t_{1/2z}, elimination half time; V_{z/F}, apparent volume of distribution; CL_{z/F}, blood clearance.

Table 4 The Main Pharmacokinetic Parameters of Monoethylglycinexylidide (MEGX) in Two Groups of Rats (N=6)

Parameters	Unit	Control Group	Study Group
AUC _(0-t)	μg/L×h	112.489 ± 28.193	128.232 ± 27.235
AUC _(0-∞)	μg/L×h	118.947 ± 31.454	133.480 ± 26.745
C _{max}	μg/L	25.032 ± 6.101	33.799 ± 6.788*
T _{max}	h	2.333 ± 0.816	2.667 ± 1.033
t _{1/2z}	h	3.791 ± 4.738	17.592 ± 20.703
V _{z/F}	L/kg	600.123 ± 953.752	1907.659 ± 2211.695
CL _{z/F}	L/h/kg	90.331 ± 28.545	77.374 ± 14.849

Note: *P<0.05 in comparison with the control group.

Abbreviations: AUC, area under the blood concentration–time curve; C_{max}, maximum blood concentration; T_{max}, peak time; t_{1/2z}, elimination half time; V_{z/F}, apparent volume of distribution; CL_{z/F}, blood clearance.

that simvastatin could competitively inhibit the metabolism of midazolam (a CYP3A4 substrate) with K_i at 10μM.²⁰ Besides, when co-administrated with simvastatin, sinomenine (a CYP3A4 substrate) experienced 1.42-fold increment of AUC_(0-t) and 1.96-fold prolongation of t_{1/2}, while apatinib (a CYP3A4 substrate) achieved 2.4-fold increment of AUC_(0-t) and 73.9% decrement of CL_{z/F}.^{20,33} Therefore, simvastatin could inhibit the activity of CYP3A4 enzyme, impairing the metabolism and excretion of lidocaine in rats, thereby resulting in pharmacokinetic alterations in terms of AUC_(0-t), AUC_(0-∞) and CL_{z/F}. Additionally, the absorption of lidocaine was not affected by simvastatin as evidenced by C_{max} value of lidocaine presenting no remarkable difference, which may be due to lidocaine administrated by subcutaneous injection rather than gavage.

Apart from CYP3A4, CYP1A2 also played an indispensable role in lidocaine metabolism.³⁴ However, CYP1A2 may have no responsibility for the interaction between lidocaine and simvastatin. Simvastatin was metabolized by CYP3A4/5 (≥80%) and CYP2C8 (≤20%), while CYP1A2, CYP2D6, CYP2C19, CYP2C9 and other CYP isoforms

were not involved, which implied that simvastatin had no affinity for CYP1A2 and thereby had no inhibitory effect on CYP1A2 activity.³⁵ Meanwhile, there had been no researches ever reported about the inhibition of simvastatin on CYP1A2 other than CYP3A4. Thus, the drug–drug interaction between lidocaine and simvastatin may involve CYP3A4 only without the participation of CYP1A2.

MEGX, formed by lidocaine N-dealkylation in human liver, also possessed the potential of antiarrhythmic and local anesthesia lower than lidocaine as well as the risk of cardiovascular and neurologic toxicity parallel to lidocaine.^{13–15} Therefore, MEGX pharmacokinetics was also studied. After the administration of simvastatin, C_{max} value of MEGX exhibited a 1.4-fold increment compared with lidocaine administrated alone. This increment was most likely due to that lidocaine metabolism and excretion, affected by simvastatin, were impaired, thereby leading to enhanced lidocaine exposure and prolonged retention time, which inferred lidocaine had more chances to form MEGX. Additionally, MEGX could be further metabolized to glycinexylidide, which may be inhibited by simvastatin and then caused the increased C_{max} value.³⁶

In conclusion, simvastatin can inhibit the metabolism of lidocaine both in vitro and in vivo, affect the pharmacokinetics of lidocaine and MEGX in rats, and may trigger pharmacodynamic alteration and side effects. Lidocaine neurotoxicity is dose-dependent, meaning the higher lidocaine plasma concentration could increase the risk of neurotoxicity. Thus, this study is full of clinically guiding significance to the concomitant use of lidocaine and simvastatin. When these two drugs are taken concurrently, more attention and necessary therapeutic drug monitoring should be paid in order to reduce the lidocaine-related side events.

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Disclosure

The authors report no conflicts of interest in this work.

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