Meclizine Metabolism and Pharmacokinetics: Formulation on Its Absorption

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Meclizine, an antihistamine, has been widely used for prophylactic treatment and management of motion sickness. However, the onset of action of meclizine was about 1 hour for the treatment of motion sickness and vertigo. A new suspension formulation of meclizine (MOS) was developed with the intention to achieve a rapid effect. To investigate the pharmacokinetics of the new MOS formulation versus the marketed meclizine oral tablet (MOT), a phase 1 pharmacokinetic study was performed in 20 healthy volunteers. In addition, an in vitro metabolic study using human hepatic microsome and recombinant CYP enzyme was also performed to determine the metabolic pathway in the human body. The plasma concentration of MOS appeared more rapidly in comparison to the MOT. The geometric mean ratios (90% confidence interval) of AUC_{0-24} and $AUC_{0-\infty}$ indicated no significant difference in bioavailability between the 2 formulations. CYP2D6 was found to be the dominant enzyme for metabolism of meclizine, and its genetic polymorphism could contribute to the large interindividual variability. In view of the similar bioavailability with a much shorter peak time of the plasma meclizine concentration from the MOS formulation, this new formulation is expected to produce a much quicker onset of action when used for the management of motion sickness.

Keywords: *Meclizine; pharmacokinetics; metabolism; CYPs*

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For many years, meclizine has been a well-accepted antihistamine for the prophylactic treatment and management of nausea, vomiting, and dizziness associated with motion sickness.[1,2] Although scopolamine is considered to be more effective than meclizine in the treatment of motion sickness, meclizine is used more frequently because of fewer adverse effects. In addition to motion sickness, meclizine can be used in the symptomatic treatment of vertigo associated with diseases affecting the vestibular system (eg, labyrinthitis, Meniere disease). As with other antihistamines, meclizine is less effective than the phenothiazines in controlling nausea and vomiting not related to vestibular stimulation. Three different formulations including capsule (25 mg, Meni-D, Seatrace), tablet (12.5, 25, 50 mg, Antivert), and chewable tablet (25 mg, Bonine, Insight) are commercial available.[3] In 2008, annual sales of meclizine in the United States were about $51 million, and meclizine was among the top 200 generics.[4]

Despite its widespread use for many decades as an over-the-counter medicine, there is a paucity of human data on its pharmacokinetics and metabolism. In one anecdotal report, a serum level of 10 ng/mL was reported at 12 hours following an oral dose of 75 mg, and the elimination half-life of the parent compound was 6 hours (data from USPID, 1994). In another report, the plasma concentration-time profile of 1 subject was described, and the AUC_{0-24} and half-life were found to be 66.6 ng/ml·h and 7 hours, respectively.[5] In rats, meclizine was distributed throughout most body tissues, found to cross the placenta, and metabolized in the liver to an inactive form, norchlorcyclizine. When give extravascularly, the drug is excreted in feces and urine unchanged or as metabolites such as norchlorcyclizine.[6-8]

The onset of action for the marketed oral meclizine tablet is about 1 hour for the treatment of motion

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sickness and vertigo.[9,10] The duration of a single dose of meclizine is about 24 hours. To achieve the best therapeutic effect, it should be taken 1 hour ahead of the motion exposure. Once motion sickness starts, the conventional meclizine tablet is unlikely to exert an appreciable anti–motion sickness effect. In an attempt to overcome this limitation (ie, to achieve a rapid onset of action), a new meclizine oral solution (MOS) was developed by Comprehensive Drug Enterprises Ltd (Hong Kong, China). In an in vivo preliminary study of comparing the suspension of the marketed meclizine with the MOS in rats, the new solution formulation was found to be stable and rapidly absorbed. In rats that had received the MOS formulation, the plasma meclizine concentration quickly increased in the first 30 minutes and was about 70% to 90% higher than the suspension formulation. These promising results indicate that the MOS is a viable alternative to currently available meclizine products and can possibly achieve faster onset as well.

To evaluate the time course of the MOS's plasma concentration in human subjects and to compare its pharmacokinetics with the current commercially available meclizine oral tablet (MOT), a clinical phase 1 study was performed. In addition, because of the lack of information on the metabolism of meclizine, a metabolic study using human pooled liver microsome as well as the recombinant CYP enzymes (rCYPs) was also carried out.

MATERIALS AND METHODS

Materials

MOS 25 mg was provided by Marching Pharmaceutical Ltd (Hong Kong, China), while the reference product, MOT 25 mg, was purchased from CVS pharmacy (Motion Sickness II). The human pooled liver microsome, recombinant CYP enzyme including 3A4, 2C9, 2C19, and 2D6 were obtained from BD (Franklin Lakes, NJ). Tris (hydroxymethyl) aminomethane, glucose-6-phosphate (G6P), β-nicotinamide adenine dinucleotide phosphate (NADP), glucose 6-phosphate dehydrogenase (G6PDH), $MgCl_2$, alamethicin, and Tris were purchased from Sigma-Aldrich (St Louis, MO).

Clinical Pharmacokinetic Study Protocol

This study was conducted using an open, single-dose, 2-sequence, 2-period, crossover, randomized design. Twenty healthy subjects were randomly assigned to 1 of 2 dosing sequences. Each subject underwent 2 study sessions, during which they received either an oral 25 mg of MOS or MOT after at least 12 hours of fasting. The 2 study sessions were separated by a washout period of at least 1week.

The study protocol and statement of informed consent were approved by the Institutional Review Board of the Western University of Health Sciences. All volunteers were fully advised of the nature, purpose, procedures, and possible risks of this study by a member of the study team. An acknowledgment of the receipt of this information and the participant's willingness to volunteer were obtained by signing the informed consent form before participating in the study.

The subjects were all nonsmokers, 18 to 60 years old, and within 25% of ideal weight. They were all in good health based on medical history, physical examination, electrocardiogram evaluation, and routine laboratory tests including blood chemistry, hematology, and urine analysis. No evidence of any major organ/system disease including lung, hepatic, and cardiac disease was identified within 3 months prior to the study. A negative pregnancy test and nonlactating status were required for women. All participants were required not to take ethanol or caffeinated beverages during each study period prior to the study and during the study.

During each study session, venous blood samples were collected at predose (0 hours); then at 5, 10, 15, 30, 45, 60, and 90 minutes; and 2, 3, 4, 6, 8, 12, and 24 hours postdose. At each time point, 4 mL of blood was drawn and stored in a sodium heparin tube. All blood samples were stored at 4 °C immediately and then centrifuged at 4000 rpm for 10 minutes at 4 °C within 1 hour. Afterward, the separated plasma samples were transferred into 2 polypropylene tubes and stored at –80 °C until assay.

The plasma concentration of meclizine was determined using a validated HPLC-MS/MS method.[11] The plasma concentration-time data were analyzed by noncompartmental method (with the aid of WinNonlin software, version 2.1, SCI). The following pharmacokinetic parameters were generated:

- C_{max}: Peak drug concentration, obtained directly from the original concentration-time data
- T_{max}: Time to peak drug concentration, obtained directly from the original concentration-time data
- $AUC_{0\text{-}24}$: Area under the concentration-time curve from time zero to the last sampling time 24 hours
- $AUC_{0\text{-}\infty}$: Area under the concentration-time curve from time zero to infinity, where $AUC_{0\text{-}\infty} = AUC_{0\text{-}24} + C_{24}/\lambda z$, where λz refers to the terminal phase elimination rate constant
- $T_{1/2}$: Terminal elimination half-life, calculated as $0.693/\lambda z$

CL/F: apparent oral clearance, calculated according to CL/F = Dose/$AUC_{0-\infty}$

V_d/F: apparent volume of distribution, calculated according to Vd/F = (CL/F)/λz

Statistics

Analysis of variance (ANOVA) was performed on C_{max}, T_{max}, AUC_{0-24}, $AUC_{0-\infty}$, and $T_{1/2}$. The statistical model included the following sources of variation: sequence, subject (nested in sequence), period, and treatment. The sequence effect was tested using the between-subject main effect as an error term. All other main effects were tested against the residual error from the ANOVA. The 90% confidence intervals for the differences in the means of AUC_{0-24}, $AUC_{0-\infty}$, and C_{max} between the 2 products were calculated using 2 one-sided *t* tests.

Differences in T_{max} and $T_{1/2}$ were compared between the 2 formulations using a Wilcoxon signed-rank test and paired Student *t* test, respectively.

Metabolism Study

The metabolism of meclizine by hepatic microsome as well as recombinant cytochrome P450 (CYP) enzyme including CYP 3A4, 2C9, 2C19, and 2D6 was performed in a reaction mixture containing an NADPH-generating system (3.3 mM G-6-P, 1.3 mM NADP, 3.3 mM $MgCl_2$, and 0.4 U G-6-PDH, 25 μg/mL alamethicin), hepatic microsome, or recombinant CYP enzymes (0.5 mg/mL). The reaction mixture was preincubated for 2 minutes at 37°C. The stock solution of meclizine at concentrations of 10 uM, 100 uM, and 1 mM were added to generate the final concentrations of 100 nM, 1000 nM, and 10 000 nM. The reaction was quenched by the addition of 3 volume of acetonitrile at time points of 0, 15, 30, and 60 minutes. The incubation mixture was vortexed for 1 minute and then centrifuged at 10 000 rpm for 5 minutes. An aliquot of the supernatant was analyzed using the HPLC-MS/MS method to detect the residual meclizine.[11] The velocity of reaction was expressed as the amount of meclizine disappeared for a unit of time. The samples were prepared in triplicate, and data were expressed as mean ± standard deviation (SD).

To measure the enzyme kinetic parameters, different concentrations of meclizine (ranging from 0.05 μM to 10 μM) were incubated with the liver microsome as well as the rCYPs using the method as mentioned above, with an incubation time of 1 hour. The kinetic parameters V_{max} and km were calculated using Prism 5.0 (GraphPad Software, Inc, San Diego, CA) by nonlinear regression. These values were used to calculate the intrinsic clearance value (V_{max}/km). The results are expressed as mean ± standard error (SE) for 5 replicates.

The 1-hour microsome sample was used to identify the potential metabolites. The samples were separated using the same HPLC method mentioned above, and the elution underwent the full mass scan from 50 to 500 m/z using the positive ion mode. Based on the full mass data, selected ion monitoring was performed to confirm the accurate masses of the precursor ion(s) of potential metabolite(s).

RESULTS

Twenty nonsmoking subjects were enrolled. Their mean age was 26.7 ± 4.7 years (range, 22-40 years), and their mean weight was 70.6 ± 11.8 kg (range, 51.8-92 kg). All of the subjects completed the study, but 1 subject was later found to have consumed a caffeinated beverage prior to dose 1 and was excluded from the data analysis due to protocol violation.

The mean plasma concentration-time data of meclizine following an oral dose of MOS or MOT in 19 subjects are shown in Figure 1. The corresponding pharmacokinetic parameters are summarized in Table I.

The mean values of C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ between the 2 products are shown in Table II. The geometric mean ratios (90% confidence interval [CI]) of C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ were 132.98% (121.22%-145.88%), 104.15% (95.56%-112.33%), and 103.64% (96.20%-111.65%), respectively, for MOS 25 mg versus MOT 25 mg. No significant sequence, period, or treatment effects on the $T_{1/2}$, AUC_{0-24}, and $AUC_{0-\infty}$ were observed ($P > .05$, 1-way ANOVA). However, significant subject effect and treatment effects were observed on C_{max} and T_{max}. The median T_{max} of MOS was 1 hour (0.5 to 4 hours), which was significantly shorter than that of MOT, which was 3 hours (1.5 to 6 hours; $P = .001$, Wilcoxon signed ranks test). The mean C_{max} in the MOS group was greater than that of the MOT group (99.43 ± 48.34 vs 80.07 ± 51.85 ng/mL for MOS and MOT, respectively, $P = .001$, paired-sample *t* test).

No formulation-related difference was observed in the mean $T_{1/2}$ value of meclizine ($P = .885$, paired-sample *t* test). The mean $T_{1/2}$ of meclizine was 5.24 ± 0.82 hours and 5.21 ± 0.80 hours, respectively, for MOS 25 mg (test) and MOT 25 mg (reference), respectively.

The metabolism of meclizine from human pooled liver microsome and the rCYPs are shown in Figure 2. The amount of the parent meclizine was decreased substantially by CYP2D6 or liver microsome as compared with other rCYPs. The enzymatic kinetic data are presented in Figure 3 and Table III.

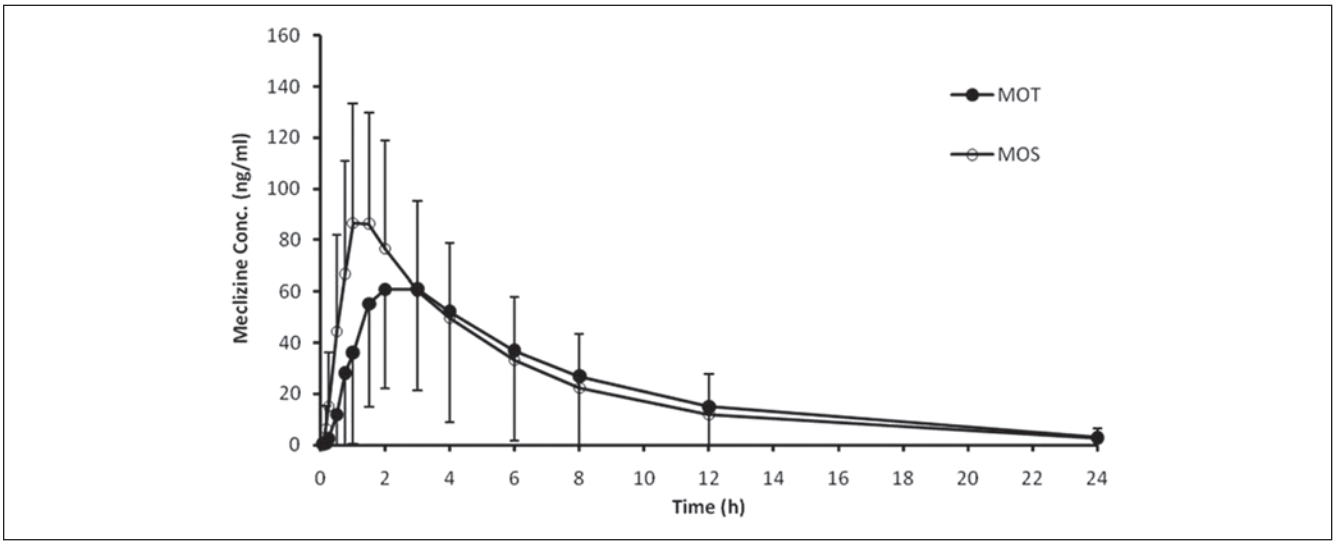

Figure 1. The meclizine plasma concentration-time course of human subjects after receiving a single dose of meclizine oral tablet (MOT; 25 mg) or meclizine oral solution (MOS; 25 mg).

Table I Pharmacokinetic Parameters After Receiving 25 mg of Meclizine Oral Tablet (MOT) or Meclizine Oral Solution (MOS)

	MOS	MOT
T_{max}, h	1.28 ± 0.74	3.11 ± 1.35
C_{max}, ng/mL	99.43 ± 48.34	80.07 ± 51.85
$T_{1/2}$, h	5.24 ± 0.82	5.21 ± 0.80
CL/F, L/h/kg	0.14 ± 0.02	0.14 ± 0.02
Vd/F, L/kg	6.40 ± 3.29	6.78 ± 3.52
AUC_{0-24}, ng·h/mL	542.00 ± 410.53	544.29 ± 511.62
$AUC_{0-\infty}$, ng·h/mL	564.03 ± 439.96	566.54 ± 534.75

Table II Ratios and 90% Confidence Interval (CI) of Pharmacokinetic Parameters Between Meclizine Oral Solution (MOS) and Meclizine Oral Tablet (MOT)

Parameter	Geometric Mean (MOS)	Geometric Mean (MOT)	Geometric Mean Ratio (T/R)	90% CI
C_{max}	90.99	68.42	132.98	121.22-145.88
AUC_{0-24}	465.04	446.52	104.15	95.56-112.33
$AUC_{0-\infty}$	481.42	464.53	103.64	96.20-111.65

A precursor ion with m/z of 407 was identified in the microsome samples, which is 16 Da greater than the meclizine $[M+H]^+$ (m/z: 391). This result suggested the oxidative metabolite was identified with the addition of an oxygen group, although its chemical structure needs to be further identified.

DISCUSSION

The results of the present study indicated that the new oral solution (MOS) has a much shorter T_{max} than the marketed tablet (MOT) without a significant difference in the total drug exposure. In addition, the $T_{1/2}$ of both

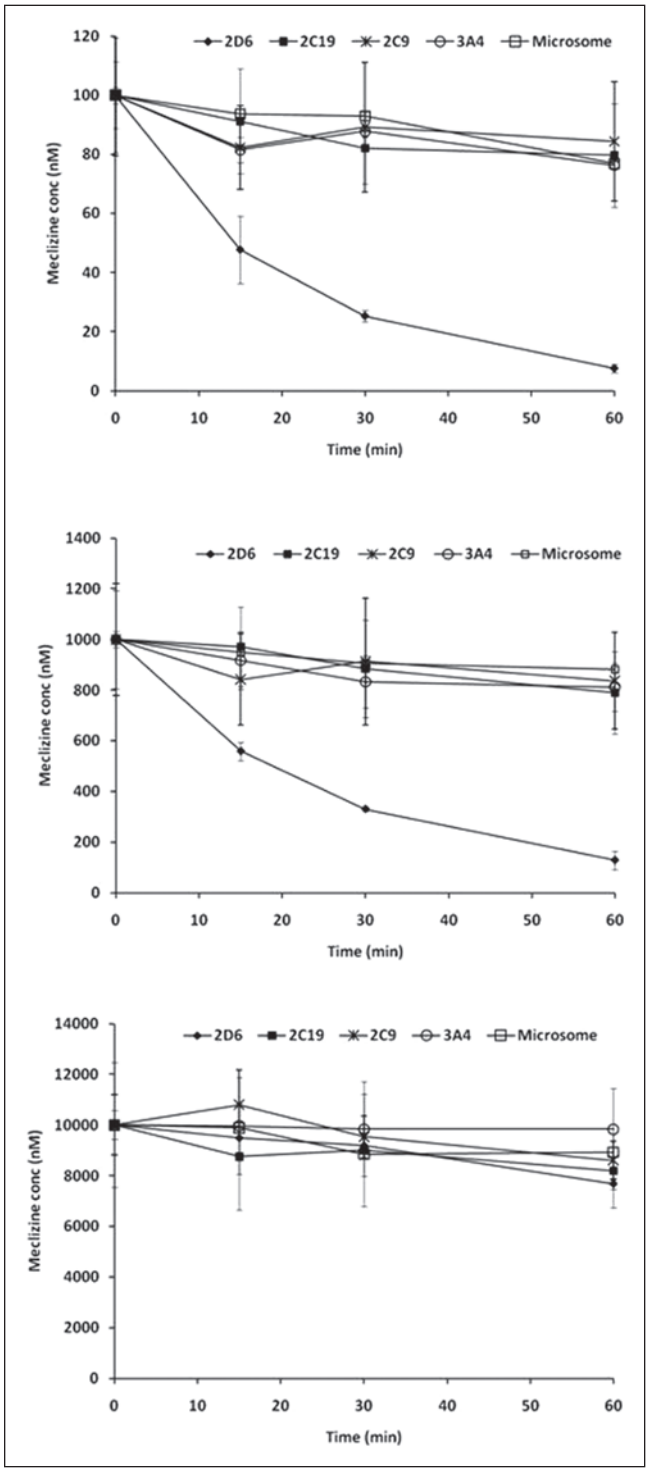

Figure 2. The decrease of meclizine concentration versus time when incubated with human liver microsome and 4 types of rCYP enzymes including 2C9, 2C19, 2D6, and 3A4. Each data point was expressed as mean ± SD (n = 3).

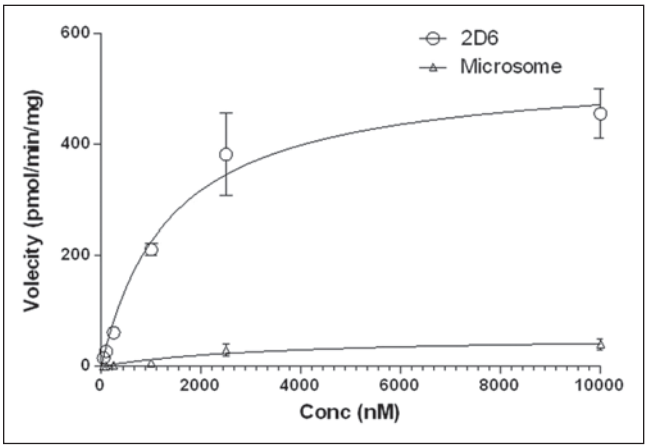

Figure 3. The decreasing rate of the amount of meclizine versus its concentration when incubated with human liver microsome or CYP 2D6. Each data point was expressed as mean ± SE (n = 5).

formulations was similar, which suggests there was no difference in the elimination of meclizine with these 2 formulations. These results suggested that the new formulation (MOS) changed only the absorption rate but not the extent or drug disposition. In view of similar bioavailability but much shorter peak time of the plasma meclizine concentration of the MOS formulation, this new liquid formulation is expected to produce a much quicker onset of action than the existing tablet formulation when used for the management of motion sickness.

The 90% CIs of the geometric mean test/reference ratios for C_{max} (121.22%-145.88%) were slightly outside the upper limit of the accepted 70% to 143% range as per the World Health Organization guideline. In view of a relatively safe profile from a wide range of meclizine doses used clinically and lack of clear relationship of C_{max} with adverse effects (up to 225 mg/d for 9.5 years with no adverse effects reported),[12] it is reasonable to view these 2 formulations to be therapeutically bioequivalent since there was no significant difference in AUC.

The present study, for the first time, provided metabolism and kinetic data for meclizine in human preparations. CYP2D6 was found to be the dominant hepatic enzyme for the metabolism of meclizine. Previously, an inactive metabolite, norchlorcyclizine, was identified in rat studies, and 10 metabolites were identified in human feces and urine.[7,8] However, we did not detect such metabolites when using human hepatic microsome or recombinant-specific CYP enzymes.

Table III Enzyme Kinetic Properties of Meclizine

Treatment	V_{max}, pmol/min/mg	Km, nM	Clint, mL/min/mg
rCYP 2D6	536.80 ± 25.94	1385.00 ± 207.10	0.39
Microsome	55.82 ± 8.59	3447.00 ± 1299.00	0.02

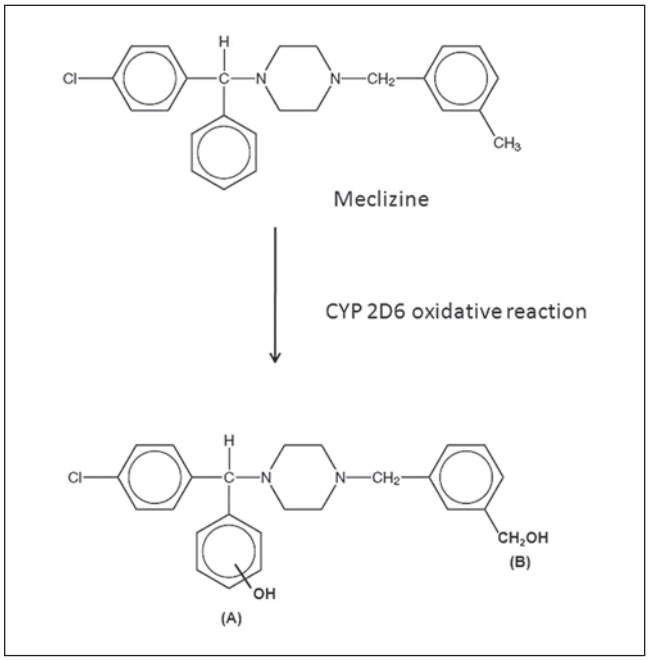

Figure 4. Metabolic pathway of meclizine when incubated with human liver microsome or CYP2D6 forming either (A) aromatic hydroxylation or (B) benzylic oxidation stopping at hydroxymethyl metabolite.

Although the exact structure of the metabolite determined from our study is unknown, based on our LC/MS/MS data, the metabolite should be one of the oxidative metabolites (see Figure 4) of which aromatic hydroxylation is the most likely one. Further work is needed to confirm the exact structure.

Our human pharmacokinetic data indicated that the interindividual variations of AUC and $T_{1/2}$ were larger than that of the intraindividual variations (CVs of AUC were 98% and 19%, $T_{1/2}$ 18% and 8% for interindividual and intraindividual variability, respectively). The calculated genetic contribution (rGC) of variability among different individuals is 0.96 and 0.80 for AUC and $T_{1/2}$, respectively, which suggested that significantly different genetic components may contribute to the intersubject variability. Since our study found CYP 2D6 to be the major enzyme for meclizine metabolism, its polymorphism could contribute to the observed rGC. CYP2D6 polymorphism with alleles from *1 to *78 (http://www.cypalleles.ki.se/cyp2d6.htm) is well known. These alleles can be divided into 3 types: extensive metabolizer (EM; with the major alleles of *1 and *2), poor metabolizer (PM; with the major alleles of *3 to *6), and intermediate metabolizer (IM; with the major alleles of *10 and *41).[13] Although the PM phenotype is present in only 3% to 10% of Caucasians and in less than 1% of Asians, the IM phenotype frequently exists in the Asian population (~50%).[13-15] In our study, 8 patients were of Chinese ethnic origin and 5 were Caucasians. Our study population could have contributed to the genetic variations leading to the variability of the $T_{1/2}$ observed.

CONCLUSION

A newly developed suspension formulation of meclizine provided a significantly earlier peak time in comparison to a marketed tablet formulation. This could result in an earlier onset of effect and maybe an advantage for the treatment of motion sickness.

Our metabolism study showed CYP2D6 to be the dominant enzyme for metabolism of meclizine. The polymorphism in CYP2D6 may contribute to variation in meclizine elimination observed this study.

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REFERENCES

1. Antivert oral tablets, meclizine hydrochloride [product information]. New York, NY: Pfizer; 1999.

2. Paul MA, MacLellan M, Gray G. Motion-sickness medications for aircrew: impact on psychomotor performance. *Aviat Space Environ Med*. 2005;76(6):560-565.

3. American Hospital Formulary Service, Board of American Society of Health-System Pharmacists. American Hospital Formulary Service Drug Information. Bethesda, MD: American Hospital Formulary Service; 2009.

4. 2008 top 200 generic drugs by retail dollars. *Drug Topics*. 2009:1-3.

5. Fouda HG, Falkner FC, Hobbs DC, Luther EW. Selected ion monitoring assay for meclizine in human plasma. *Biomed Mass Spectrom*. 1978;5(8):491-494.

6. Chovan JP, Klett RP, Rakieten N. Comparison of meclizine levels in the plasma of rats and dogs after intranasal, intravenous, and oral administration. *J Pharm Sci*. 1985;74(10):1111-1113.

7. Goenechea VS, Rucker G, Brzezinka H, Hoffmann G, Neugebauer M, Glanzmann G. Biotransformation of meclizine in the human body. *J Clin Chem Clin Biochem*. 1988;26(2):105-115.

8. Narrod SA, Wilk AL, King CT. Metabolism of meclizine in the rat. *J Pharmacol Exp Ther*. 1965;147:380-384.

9. AMA Department of Drugs. *AMA Drug Evaluations*. 6th ed. Chicago, IL: American Medical Association; 1986.

10. Martindale RJ, ed. *The Extra Pharmacopeia* [CD-ROM version]. Englewood, CO: Micromedex; 1997.

11. Wang Z, Qian S, Zhang Q, Chow MSS. Quantification of meclizine in human plasma by high performance liquid chromatography-mass spectrometry. *J Chromatograph B*. 2011;879:95-99.

12. Meclizine, Drugdex, Micromedex® Healthcare series 2009. www.thomsonhc.com.

13. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I. *Clin Pharmacokinet*. 2009;48(11): 689-723.

14. Neafsey P, Ginsberg G, Hattis D, Sonawane B. Genetic polymorphism in cytochrome P450 2D6 (CYP2D6): population distribution of CYP2D6 activity. *J Toxicol Environ Health Part B*. 2009;12(5/6):334-361.

15. Sistonen JA, Sajantila AA, Lao OC, Corander JB, Barbujani GG, Fuselli SAD. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. *Pharmacogenet Genom*. 2007;17(2):93-101.