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Prevalence of desloratadine poor metabolizer phenotype in healthy Jordanian males

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ABSTRACT: *Purpose:* To study the prevalence of desloratadine slow metabolizer phenotype among a group of healthy Jordanian male volunteers.
Methods: A total of 62 healthy Jordanian male volunteers were included in this study. A single 5 mg desloratadine oral tablet was given and blood samples were taken to determine the desloratadine and 3-hydroxydesloratadine (3-OH-desloratadine) concentrations using a specific liquid chromatography-mass spectrometric method (LC/MS/MS). The determination of pharmacokinetic parameters of all the individuals was determined by using Kinetica® program version 4.1. Poor metabolizers or slow metabolizers of desloratadine were determined as individuals having a 3-OH-desloratadine to desloratadine exposure ratio lower than 10% or a desloratadine half-life $\geq$ 50 h.
Results: Among the 62 volunteers who participated in the study there were only two volunteers who were labeled as desloratadine slow metabolizers, giving a prevalence of 3.2%. The maximum plasma concentrations (C_{max}) were similar in the extensive and slow metabolizers groups but a longer time (t_{max}) was needed to achieve this concentration in one of the volunteers who was a desloratadine slow metabolizer.
Conclusion: The incidence of the poor metabolizer phenotype of desloratadine in the Jordanian population studied is similar to certain ethnic groups (e.g. Asian, Caucasians and Hispanic); however, it is lower than other populations (e.g. American Indians and Black). Copyright © 2012 John Wiley & Sons, Ltd.

Key words: desloratadine; poor metabolizers; phenotype; Jordanians

Introduction

Desloratadine is a non-sedating long-acting tricyclic with selective H_1-receptor histamine antagonist activity. The drug is indicated for the relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal and perennial) and for the relief of symptoms associated with chronic idiopathic urticaria in children and adults [1–4]. Desloratadine is rapidly absorbed, has dose-proportional pharmacokinetics, and has a half-life range of 19.5 to 27 h [5–7]. The absorption of desloratadine is not affected by food, and the metabolism and elimination are not significantly affected by the subject's age, race, or sex [1,5,8–10]. There are no clinically relevant interactions between desloratadine and erythromycin, ketoconazole, or grapefruit juice [1,11–13].

Desloratadine is extensively metabolized in human to 3-hydroxydesloratadine (3-OH-desloratadine), an active metabolite, both are subsequently glucuronidated and excreted in urine [14,15]. Using pooled human liver microsomes, neither desloratadine nor 3-OH-desloratadine inhibited

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CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 [16]. An *in vitro* study with recombinant human UDP-glucuronosyltransferases demonstrated that the *in vitro* glucuronidation of 3-OH-desloratadine is mediated primarily via UGT1A1, UGT1A3 and UGT2B15 in human liver [14].

Despite the fact that the enzyme(s) involved in the formation of 3-OH-desloratadine are not yet identified, phenotypic polymorphism in the metabolism of desloratadine has been identified [7]. Some individuals have a lower ability to form the major metabolite of desloratadine and are thus termed as desloratadine poor metabolizers or slow metabolizers of desloratadine; i.e. any individual having a 3-OH-desloratadine to desloratadine exposure ratio lower than 10% or a desloratadine half-life ≥ 50 h [7].

Although, desloratadine has a safety profile similar to placebo and it is well tolerated, desloratadine poor metabolizers may be at risk of toxicity and adverse effects due to the prolonged and high exposure to desloratadine especially with repeated doses [7].

In a review study by Prenner *et al*. [7], data from a total of 3748 subjects were examined: children aged 2–11 years ($n = 2554$) and adults aged 12–70 years ($n = 1194$). The prevalence of the desloratadine poor metabolizer phenotype ranged from 0–17% in different ethnic groups [7]. Overall, desloratadine caused no change in the frequency or profile of adverse events, nor are there changes in ECG parameters in adults or children who are desloratadine poor metabolizers. However, in certain ethnic groups that have high prevalence of desloratadine poor metabolizers further studies on the safety and tolerability of desloratadine are justified [7].

In view of the fact that the metabolic pathway of desloratadine is not fully elucidated and the metabolism of desloratadine is polymorphic in different populations, this study was carried out.

Jordan is a developing Middle Eastern country of 5.3 million people. The population in Jordan comprises mainly Arabs, with small communities of Chechen, Circassains, Armenians and Kurds that represent less than 1% of the population [17]. Although the prevalence of the desloratadine poor metabolizer phenotype has been reported in many different ethnic groups [7], so far, no information is available for the Jordanian population. The aim of this study was to investigate the presence and to determine the prevalence of desloratadine poor metabolizers in healthy Arab Jordanian males, as gender has no apparent effect on the drug's metabolism and elimination [10].

Materials and Methods

A single 5 mg tablet of desloratadine (Aeriustm®) was given to 62 healthy unrelated male Arab Jordanians in a study conducted by the International Pharmaceutical Research Centre (IPRC). The study was performed in accordance with the declaration of Helsinki (Washington, USA, 2004) and current Good Clinical Practice (GCP) guidelines and was approved by the ethics committee; the institutional review board (IRB) of IPRC in Amman, Jordan. The study was also approved by Jordan Drug and Food Administration (JFDA). All volunteers, consented in writing, were selected according to the following inclusion criteria: male, age 18–45 years (26 ± 6.29 years), body weight within the limit for height (174 ± 6.38 cm, 75 ± 12.68 kg); non smoker; no drug or alcohol abuse; no history of contraindication and/or allergy to the drug and any related compounds; normal physical and clinical examinations including vital signs, hepatic, renal, respiratory, cardiac, gastrointestinal and psychiatric; normal clinical laboratory tests including biochemistry, hematology, routine urine analysis; negative for HIV, hepatitis B and C; no consumption of drugs for 2 weeks prior to the study; no blood donation, hospitalization or participation in any study clinical within the past 2 months of initiation of the present study. The study's subjects were confined at the clinical site 14 h before dosing until 24 h post dosing. The drug was administered with 240 ml of water after an overnight fasting of 10 h. No water was permitted 2 h before and after dosing. A standard lunch was served to the volunteers 4 h after dosing. Xanthine containing products were not allowed 2 days before dosing. Seven ml of blood samples were withdrawn via an indwelling cannula placed in the forearm antecubital vein. Blood samples were withdrawn at zero time (predose), and then at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.50, 9.00, 12.00, 24.00, 48.00 and 72.00 h post dosing (a total of 18 blood samples

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were collected from each volunteer). The blood samples were immediately centrifuged for 10 min at 1789 × *g*. The plasma samples were stored immediately at −20 °C.

The concentrations of desloratadine and its metabolite (3-OH-desloratadine) in volunteers' plasma were determined by a specific liquid chromatography-mass spectrometric method (LC/MS/MS). The technique was developed and validated at the IPRC laboratories. The procedure involved a simple liquid–liquid extraction technique of desloratadine, its metabolite and their corresponding internal standards (IS), desloratadine-D4 and 3-OH desloratadine-D4, with diethyl ether. Samples then were evaporated under nitrogen stream and reconstituted in mobile phase. Separation was accomplished by an HPLC system using a C18 column and ammonium formate buffer/acetonitrile and formic acid as the mobile phase. Detection was carried out on an Applied Biosystems API 4000 mass detector (Applied Biosystems, Canada) by multiple reaction monitoring mode. The ionization was optimized using a turbo ion spray source in the positive mode (TIS+), while selectivity was achieved by MS/MS analysis. Chromatograms of desloratadine were extracted at m/z: 311.20 > 259.25; while for 3-OH-desloratadine were at m/z: 327.30 > 275.20. Desloratadine-D4 chromatograms were extracted at m/z: 315.25 > 263.25, while 3-OH desloratadine-D4 chromatograms were extracted at m/z: 331.30 > 279.20. The method was designed to cover the linearity over the working range of 0.05–6 ng/ml for desloratadine and 3-OH-desloratadine in human plasma.

The LC/MS/MS method was shown to be linear for desloratadine determination over the range 0.05–6 ng/ml ($r^2 > 0.99$). The results were within the accepted criteria as stated in the aforementioned USFDA guideline [18]. The method proved to be sensitive and specific by testing six different human plasma batches.

The LC/MS/MS method was also proved linear for 3-OH-desloratadine over the range 50–6000 pg/ml ($r^2 > 0.99$). The lower limit of quantitation LLOQ proved to be 50 pg/ml with 100.00% accuracy and 7.34% CV. Intra-day accuracy ranged 100.44–95.59% (CV% 6.98–2.46); whereas inter-day accuracy ranged between 98.93% (CV 11.23%) and 99.87% (CV 5.05%). Mean recovery was 71.58% with a precision of 6.69%. Plasma samples were proved stable for 6 h at room temperature 105.16% (CV 4.27%), and for four cycles of freeze and thaw 96.27% (CV 1.68%), and for 60 days at −20 °C 96.53% (CV 3.44%).

The determination of pharmacokinetic parameters of all individuals was determined by using Kinetica® program version 4.1 (Thermo Electron Corporation; USA). Plasma profiles were best characterized by a non-compartmental model. The elimination rate constant (λZ) was obtained as the negative of the slope of the linear regression of the log transformed concentration values versus time data in the terminal phase. The elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda Z$. The area under the curve to the last measurable concentration ($AUC_{0\text{-}t}$) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity ($AUC_{0\text{-}\infty}$) was calculated as $AUC_{0\text{-}t} + C_t/\lambda Z$, where C_t is the last measurable concentration.

Results

Desloratadine was well tolerated by all volunteers. No incidence of side effects or adverse reactions was observed during the study. The same volunteers who started the study participated to the end of the study. All the volunteers left the study without any change in their baseline parameters.

The described analytical method was proven sensitive and accurate for the determination of desloratadine and its metabolite in human plasma. The combination of LC (under the isocratic conditions described) with ESI+/MS/MS leads to short retention times and yields high selectivity and sensitivity. No interferences with the analytes were observed due to the high selectivity of the LC/MS/MS technique. No ion suppression effects were observed.

Two volunteers (2/62) were identified as poor metabolizers of desloratadine as 3-OH-desloratadine was not detected in one volunteer (volunteer no 34) and the 3-OH-desloratadine to desloratadine exposure ratio of the second was < 10% (3.4%, volunteer no 58). This is calculated as a prevalence of desloratadine poor metabolizer phenotype of 3.2% in our study population (2/62).

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The pharmacokinetic parameters of desloratadine for the 60 extensive and the two poor metabolizers are shown in Table 1. The plasma concentration–time profiles of desloratadine after a single dose of 5 mg tablet to 60 healthy subjects and volunteers no 34 and 58 are presented in Figure 1 (mean ± SD) and Figure 2, respectively. An apparent secondary peak was clearly detected in Figure 1.

The mean maximum plasma concentration (C_{max}) of desloratadine was 2.35 ± 0.84 ng/ml (range 1.00–4.39 ng/ml) and was observed at 3.81 ± 1.49 h (range 1.00–7.50 h) post dose. The C_{max} of the two slow metabolizers were 2.10 and 2.07 ng/ml, respectively, similar to that of the extensive metabolizers (2.35 ± 0.84 ng/ml) but it was reached at a slower rate for volunteer no 34 (t_{max} was 12.00 h). In extensive metabolizers the half-life of elimination of desloratadine ($t_{1/2}$) was slow and ranged from 6.37 to 36.42 h (20.88 ± 6.41 h), while it was not determined in the two volunteers that were marked as slow metabolizers of desloratadine. As differences exist in the $AUC_{0\rightarrow72}$, the systemic exposures to desloratadine in the slow metabolizers were 2.5–2.7-fold higher than the mean exposure in the extensive metabolizers.

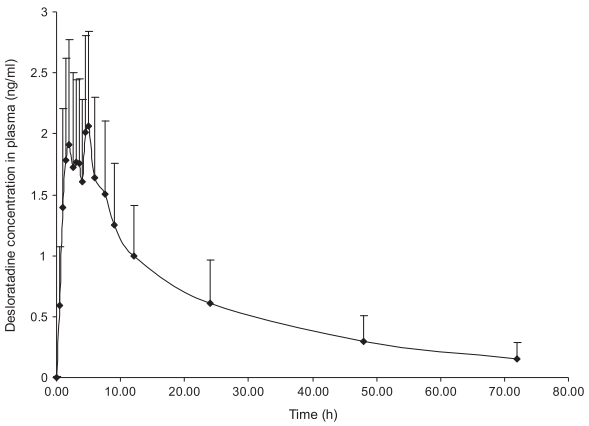

Figure 1. Mean plasma concentration–time profiles of desloratadine after a single dose of 5 mg tablet to 60 healthy subjects (mean ± SD)

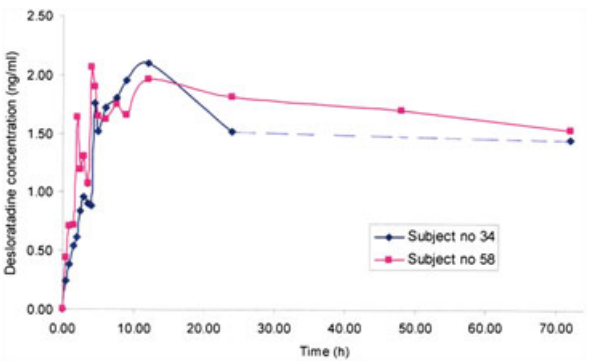

Figure 2. The plasma concentration–time profiles of desloratadine after a single dose of 5 mg tablet to volunteer no 34 and volunteer no 58

Discussion

The results from clinical pharmacology studies show that after oral administration, desloratadine is well absorbed with maximum plasma drug concentrations achieved at approximately 2–4 h post-dose. The drug has a plasma elimination half-life in the range 19.5–27 h, which supports once daily dosing [5–7,9,19], this is comparable to the $t_{1/2}$ observed in our population for the extensive metabolizers which was 20.88 ± 6.41 h. A secondary peak was clearly detected in Figure 1. This observation was also reported by others [6].

Phenotypic polymorphism in the metabolism of desloratadine has been observed [6,7]. Some

Table 1. The mean ± SD of the pharmacokinetic parameters after single dose administration of one tablet of 5 mg desloratadine in healthy Arab male volunteers

		Desloratadine		
Parameter	Unit	Extensive metabolizers (mean ± SD, $n = 60$)	Poor metabolizer (volunteer no 34)	Poor metabolizer (volunteer no 58)
C_{max}	ng/ml	2.35 ± 0.84	2.10	2.07
$AUC_{0\rightarrow72}$	ng.h/ml	44.41 ± 20.01	111.759	121.65
t_{max}	h	3.81 ± 1.49	12.0	4.00
$t_{1/2}$	h	20.88 ± 6.41	Not determined	Not determined

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individuals have lower ability to metabolize desloratadine to its major metabolite (3-OH-desloratadine), i.e. the exposure ratio of 3-OH-desloratadine to desloratadine is less than 10%, or a desloratadine half-life of 50 h or higher [7]. To date, enzymes responsible for the formation of 3-OH-desloratadine remain unknown and need to be elucidated. However, the enzyme(s) responsible for glucuronidation of desloratadine and 3-OH-desloratadine were identified as UGT1A1, UGT1A3, UGT2B15 [6,14].

The pharmacokinetic parameters of the extensive metabolizers in the Jordanian population (Table 1) were within the results that have been reported in the literature. The C_{max} concentration found in our study group was 2.35 ± 0.84 ng/ml (range 1–4.39 ng/ml) which is comparable to the C_{max} concentrations reported with the same dose (range 3.30–4.32 ng/ml [1,5,6,9,19]). The C_{max} concentrations obtained for the desloratadine slow metabolizers in our population were 2.07 and 2.10 ng/ml which is similar to the extensive metabolizers but was reached at a slower rate for one volunteer, the same finding was reported by Ramanathan *et al*. [6].

Depending on the timing of the last dose, several different values of *AUC*s for desloratadine were reported by different researchers [1,6,7,19]. In our study, a tendency of a lower *AUC* value in extensive metabolizers compared with the *AUC* values in desloratadine poor metabolizers was noticed; i.e. lower systemic exposure to desloratadine. This finding was similar to the observation made by others [6,7].

Two volunteers were labeled as desloratadine slow metabolizers (no metabolite was detected in volunteer no 34 and volunteer no 58 had a 3-OH-desloratadine to desloratadine exposure ratio of $< 10\%$ [7]). As the metabolite was not detected, C_{max} and $AUC_{0\rightarrow72}$ values for 3-OH-desloratadine were not estimated in volunteer no 34 (Table 2). Whereas, in volunteer no 58 the C_{max} and $AUC_{0\rightarrow72}$ values for 3-OH-desloratadine were 0.185 ng/ml and 4.14 ng.h/ml, respectively. The findings support the fact that lower concentrations of the metabolite are formed in desloratadine slow metabolizers. Prenner *et al*. [7] reported C_{max} concentrations for desloratadine extensive and poor metabolizers in adults and children in the range 0.79–1.64 and 0.12–0.20 ng/ml, respectively, both are similar to our C_{max} values in extensive and slow metabolizers (1.06 and 0.185 ng/ml, respectively).

Although the number of volunteers was relatively small ($n = 62$), two volunteers had a 3-OH-desloratadine to desloratadine exposure ratio of 10% and hence were identified as desloratadine poor metabolizers in our study group, i.e. the prevalence of desloratadine poor metabolizers was 3.2% (2/62 volunteers) in healthy adult Jordanian males. This is similar to the prevalence of the poor metabolizer phenotype in the total population (6% in both adults and children, $n = 3748$), Asian (0%, $n = 24$), Caucasian (2%, $n = 1460$) and Hispanic (2%, $n = 1063$) and lower than American Indian (8%, $n = 49$) [7]. Conversely, it is much lower than the desloratadine poor metabolizer phenotype expressed in the Black population (17%, $n = 990$ [7]).

The desloratadine safety profile has been found to be similar to placebo, even in poor metabolizers of desloratadine that have higher exposure to desloratadine [7]. No changes in ECG parameters were shown in adults and children who are poor metabolizers; this indicates the cardiac safety of

Table 2. The mean ± SD of the pharmacokinetic parameters of 3-OH-desloratadine after single dose administration of one tablet of 5 mg desloratadine in healthy Arab male volunteers

		3-OH-Desloratadine		
Parameter	Unit	Extensive metabolizers (mean ± SD, $n = 60$)	Poor metabolizer (volunteer no 34)	Poor metabolizer (volunteer no 58)
C_{max}	ng/ml	1.06 ± 0.52	Not determined[a]	0.185
$AUC_{0\rightarrow72}$	ng.h/ml	22.68 ± 7.95	Not determined[a]	4.14
t_{max}	h	4.23 ± 1.46	Not determined[a]	4.00
$t_{1/2}$	h	26.10 ± 9.03	Not determined[a]	42.59

[a]Not determined as the metabolite was not detected in the plasma of this individual.

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this drug [7]. Although desloratadine is well tolerated, in certain ethnic groups with higher incidence of the poor metabolizers phenotype further studies are needed to establish the safety and tolerability of desloratadine.

Depending on the low prevalence of desloratadine poor metabolize phenotype in the Jordanian population, i.e. 3.2% in our study group, it can be concluded that the use of desloratadine is relatively safe in Jordanians.

Conclusions

This study provides the first report on the prevalence of desloratadine poor metabolizer phenotype in the Jordanian population and indicated that only 3.2% (2/62 volunteers) are poor metabolizers which is similar to that reported in the general population. This low incidence of poor metabolizers and the fact that desloratadine is well tolerated as reported by many [7,20], have shown that the use of desloratadine in the Jordanian population is safe. Clinical studies, similar to this, that involve the dosing of healthy volunteers are important as the metabolic pathway of desloratadine is not fully characterized and the metabolism of this drug is polymorphic in many populations.

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Conflict of Interest

The authors report no declarations of interest.

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