Rosuvastatin pharmacokinetics in Pakistani healthy volunteers in comparison with other population

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Abstract: In current study, the pharmacokinetics (PK) of rosuvastatin were evaluated in Pakistani healthy volunteers and compared with those reported in other population. This was a randomized and open labeled clinical trial in which a single oral dose of 40 mg rosuvastatin was administered to the overnight fasted healthy volunteers. Plasma concentrations of rosuvastatin were quantified by a validated liquid chromatography-tandem mass spectrometry method. The PK parameters of rosuvastatin and its metabolite N-desmethyl-rosuvastatin were determined by PK specific software i.e., PK-Summit® (PK-Solutions). A total of 20 healthy volunteers having BMI in the normal ranges were included in this study. All PK parameters were represented as mean ± SD and 95% confidence intervals of the means have been calculated. The Cₘₐₓ (29.07 ± 6.88 ng/mL), Cₘᵢₐₓ (206.65 ± 55.27 ng/hr/mL) and CL/F (3275.26 ± 1072.87 mL/hr) were slightly higher in our study, whereas the values of Vd (19377.23 ± 9114.29 mL) and tₘₐₓ (3.0 ± 0.46 hr) were comparatively smaller. Overall, the PK parameters of rosuvastatin determined in our study were in compliance with other reported. Therefore, no adjustments in the dosing schedule or dose are warranted.

Keywords: Rosuvastatin, pharmacokinetics, healthy volunteers.

INTRODUCTION

Rosuvastatin (fig. 1), is chemically bis{(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[(methyl-(methyl-sulfonyl)amino]pyrimidin-5-yl][3R,5S]-3,5-di-hydroxyhept-6-enoic acid usually administered as calcium salt. Rosuvastatin (Rosuva) launched in 2003 is synthetic, belonging to 3rd generation and the most recent statin available. It is the leading drug in the statins class having a potent inhibitory activity of 3-hydroxy-3-methylglutararyl-coenzyme A reductase (HMGCoA-R) and a greater low density lipoproteins (LDL’s) lowering effect as compared with other statins (Jones et al., 2003; McTaggart, 2003). Rosuva causes reduction in low density lipoproteins-C (LDL’s-C), total cholesterol (T-C), ApoB and triglycerides (TG’s), and elevation in high-density lipoproteins-C (HDL’s-C). It also increases LDL’s-receptor synthesis that withdraws cholesterol from circulation and decreases hepatic very low density lipoproteins (VLDL’s) output (White, 2002; McTaggart, 2003). Rosuva is used to treat hypercholesterolemia both in patients with established cardiovascular disease as well as those who are at a high risk of developing atherosclerosis (Istvan & Deisenhofer, 2001; Davidson, 2002; Olsson et al., 2002; Wierzbicki et al., 2003; McTaggart & Jones, 2008).

Pharmacokinetics of rosuva has been extensively determined in different populations but its PK data in Pakistani population is lacking. Peak plasma concentration (Cₘₐₓ) of rosuva is achieved in 3-5 hr (Martin et al., 2003b). Both Cₘₐₓ and AUC are dose proportional over the range of 10-80 mg (Martin et al., 2003c). Rosuva has an absolute oral bioavailability of ~20% and absorption is estimated to be 50%. Concomitant administration of rosuva along with food affects its rate of absorption (decreases by 20%) but not the extent. There is no effect over the steady state pharmacokinetics of rosuva by variation in the timings of administration (morning or evening) (Martin et al., 2002). Volume of distribution at steady state is 134 L and plasma protein binding is 88%. Rosuva’s plasma concentrations do not affect protein binding and is usually reversible (Martin et al., 2003b).

Rosuva undergoes metabolism to a lesser extent (approx. 10%) and forms N-desmethyrosuva as a major metabolite. The CYP2C9 isozyme is primarily involved in the metabolism of rosuva, while CYP3A4 and CYP2C19 have little contribution in metabolism. Other reported metabolite is rosuvastatin-5s-lactone (Martin et al., 2003d). NDM-Rosuva is active having HMGCoA-R inhibitory activity of 1/6 to ½ as compared with rosuva, while 5s-lactone is totally inactive having no HMGCoA-R inhibitory activity (Martin et al., 2003d). In an in vitro study, a β-1-0-acyl-glucuronide conjugate of rosuva had also been detected in human hepatocytes considered to be catalyzed by UDP gluconosyltransferases i.e., 1A1 and 1A3 (Pruksaritanont et al., 2002).
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Its terminal half-life ranged from 13-21 hr and about 90% of the administered dose was recovered in the faeces unchanged. Following IV administration, 72% of the total drug was cleared via hepatic route while the remaining eliminated via renal route (Martin et al., 2003d).

Several influx and efflux transporters are involved in the intestinal, hepatobiliary and renal transport of rosuva. Rosuva’s intestinal transport is governed by an efflux transporter i.e., breast cancer resistance protein (BCRP) (Huang et al., 2006), whereas its uptake into the human hepatocytes is mediated through organic anion transporting polypeptides i.e., OATP1B1, OATP1B3, OATP2B1 and sodium taurocholate co-transporting polypeptide (NTCP). Biliary excretion occurs through multidrug resistance protein 1 (MDR1 or P-gp), multidrug resistance associated protein 2 (MRP2), BCRP and Bile salt export protein (BSEP) (Huang et al., 2006; Kitamura et al., 2008).

As rosuva undergoes only 10% metabolism forming both NDM-rosuva and rosuva-5s-lactone, so the net formation of NDM-rosuva (active metabolite) must be less than 10%, therefore, the pharmacokinetics of rosuva is best explained by assessing the PK of parent drug only. Due to this reason almost all studies assessing PK of rosuva only discussed the ADME kinetics of rosuva with only few exceptions in which PK of either NDM-rosuva or both metabolites has been discussed. Furthermore, the maximum plasma concentration of NDM-rosuva is also very low and sometimes all PK parameters are difficult to assess in plasma samples (Cooper et al., 2002). Several studies reveal that its PK is greatly variable due to genetic polymorphism, therefore, assessment of its PK in every population is necessary. The present study accounts for the determination of pharmacokinetics of rosuva and its metabolite i.e., NDM-rosuva in healthy male Pakistani volunteers after administration of single oral dose of 40 mg.

MATERIALS AND METHODS

Trial population
The study was conducted in normal healthy male volunteers of Pakistan in accordance to “world medical association’s Declaration of Helsinki - ethical principles for medical research involving human subjects” and a written informed consent was obtained from all the participants enrolled in these studies. The ethical concerns of the protocol were approved by independent ethical committee of Department of Pharmacy, University of Peshawar-Pakistan.

Normal healthy male volunteers (n = 22) without any history of illness were included in this study. Their mean ± SD of ages, weights and heights were 26.05 ± 2.52 years (range, 22-31 years), 64.0 ± 2.47 kg (range, 60-68 kg) and 65.95 ± 1.79 inches (range, 63-69 inches), respectively. Two out of these twenty-two volunteers left the studies because of their certain personal reasons and it did not affect the trial’s data interpretation.

Inclusion criteria
Only the volunteers that possessed good health were recruited in this study. A detailed physical examination and medical history was collected from all the subjects and thorough clinical examination process was carried out. Different important biochemical tests like low density lipoproteins (LDL’s), high density lipoproteins (HDL’s), and triglycerides (TG’s) profile were evaluated and electrocardiography (ECG) was also performed for all the participants. Other clinical tests included liver function tests (LFT’s), renal function tests (RFT’s), blood pressure (BP), and blood glucose level. The normal values of these examinations and tests of all the volunteers were indicative of their good health.

Exclusion criteria
Subjects having any disease like coronary heart disease (CHD), chronic renal disease, diabetes mellitus, hepatic impairment, or any other systemic pathology were excluded from this study. Obese and smokers were also excluded as these factors contribute to the imbalance in the lipids profile. Subjects using any type of medicines and those on special diets were also excluded.

Protocol of drug administration and collection of blood samples
Each participant of the trial received a single dose of rosuva 40mg after an overnight fast with a glass of water (200 mL). Blood samples (approx. 5 cc) were collected in heparinized tubes just before the first intake of rosuva and at intervals of 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12 and 24 hours after administration of the normal oral adult dose of rosuva (40 mg). Centrifugation of the non-coagulated blood samples was performed to separate blood cells and plasma, and then stored at -80°C until analysis. Although rosuva and NDM-rosuva are stable at room temperature, care was taken to provide protection from heat and excessive light during handling and other experimental procedures.

Samples analysis
Plasma samples were analyzed for rosuva and NDM-rosuva by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) developed in our laboratory (Shah et al., 2015). The plasma samples collected and stored at -80°C were thawed at room temperature at the time of analysis and drugs were extracted with a simple one step liquid-liquid extraction procedure using acetonitrile. The compounds were efficiently separated on HiChrom® C18 (150 × 3.0 mm, 3µm; Reading, UK) column using 0.1% formic acid in acetonitrile and 0.1% formic acid in water (70:30 v/v) as a
mobile phase and pumped at a flow rate of 300 μL/min. Mass spectrometer was operated in positive ion mode with the m/z ranges set for rosuva, NDM-rosuva and atorvastatin (internal standard) as 482.1750-482.1780, 468.1590-468.1610 and 559.2595-559.2625 (amu), respectively. The capillary temperature was 275°C, whereas the source and capillary voltages were 4.5 kV and 35 V, respectively. The Auxiliary and sheath gases were 15 and 50 (arbitrarily units), respectively, and the column oven temperature and sample injection volume were 25°C and 10µL, respectively. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for rosuva were 0.1 and 0.2 ng/mL, whereas for NDM-rosuva, these were 0.03 and 0.1 ng/mL, respectively.

**Pharmacokinetic Parameters and Data Interpretation**

Various pharmacokinetic parameters were evaluated using PK-Summit software® (PK-Solutions-Ver. 2.0.2). The maximum plasma concentrations (C max) and time to reach C max (T max) were observed directly from the plasma concentration versus time profiles and measured data of rosuva and NDM-rosuva. Linear trapezoidal rule was utilized for the calculation of area under the plasma concentration–time curves from zero time to the last measurable concentration i.e., [AUC] 21, whereas extrapolated to infinity i.e., [AUC] ∞ was calculated using the equation: 

\[
[AUC]_\infty = (AUC)_{21} + C_t / Ke
\]

where C t is the last quantifiable concentration of the drug in plasma. The elimination half-life (t 1/2) was then calculated as 0.693 / Ke. Ke is the elimination rate constant determined as slope of the terminal portion of elimination phase of plasma concentration–time curve using linear least square regression.

The pharmacokinetic data of rosuva and its metabolite NDM-rosuva obtained from this study was analyzed statistically by Minitab® (ver. 17) and MS Excel®. The PK parameters were expressed as mean ± SD and 95% confidence intervals of the mean calculated by paired t-test.

**RESULTS**

**Rosuvastatin and NDM-rosuvastatin pharmacokinetics**

The plasma samples collected at various time intervals from healthy volunteers treated with 40 mg single oral dose were analyzed using the developed analytical method. The rosuva and NDM-rosuva plasma drug concentrations were plotted both on linear and semilog graph papers as a function of time (figs. 2 and 3). The error bars represents the SD from the mean plasma concentration at respective times.

The values of PK parameters like C max and t max were acquired from the curve directly, while for the calculation of [AUC] 21 and [AUC] ∞, area under the first moment curve (AUMC), volume of distribution (Vd), mean residence time (MRT), clearance (CL/F), half life (t 1/2), drug’s transfer rate constant from plasma to tissues (K 12) and from tissues to plasma (K 21) etc. a pharmacokinetic specific software called PK-Summit® was utilized. All the PK parameters were mentioned in terms of mean ± SD and 95% confidence interval of the mean. The C max calculated in our study was 29.07 ± 6.88 ng/mL, whereas the values of Vd, CL/F and t 1/2 were 206.65 ± 55.27 ng/hr/mL, 19377.23 ± 9114.29 mL, 3275.26 ± 1072.87 mL/hr and 3.0 ± 0.46 hr, respectively. All PK parameters of rosuva and NDM-rosuva calculated by Non-compartmental PK analysis are presented in tables 1 & 2.

**DISCUSSION**

The usual recommended dose of rosuva by FDA is 10-40 mg (Davidson, 2004; Wolfe, 2004). It has been established that rosuva exhibits a dose proportional pharmacokinetics and the C max and AUC values increased proportionally from 10-80 mg (r² = 0.999) (Martin et al., 2003c). Furthermore, unlike other statins, the timings of administration (i.e., morning or evening) do not influence its PK or response (Martin et al., 2002). In our study, a single dose of 40 mg was administered orally in the morning to the overnight fasted healthy male adult Pakistani volunteers. For assessing differences in population pharmacokinetics, the PK parameters of rosuva and NDM-rosuva determined in our study were compared to other populations.
The \( C_{\text{max}} \) of rosuva reported in other studies after administration of 40 mg oral dose were 10.3 ng/mL (Martin et al., 2003c), 18.8 ng/mL (Martin et al., 2003b) and 37.0 ng/mL (Olsson et al., 2002). The \( C_{\text{max}} \) of the rosuva observed in present study after administration of 40 mg possesses close resemblance with reported values (Cooper et al., 2002; Olsson et al., 2002; Cooper et al., 2003c; Simonson et al., 2003; Schneck et al., 2004; Zhang et al., 2008; Bergman et al., 2010). The \( t_{\text{max}} \) of rosuva reported in other studies after administration of 40 mg oral dose of rosuva was 5.0 hr (Martin et al., 2003c). The value of \( t_{\text{max}} \) in our study was 3.0 ± 0.46 hr that was lower compared with the other studies representing a quicker absorption of rosuva in Pakistani Population. The \( [\text{AUC}] \) values for rosuva reported in other studies after 40 mg dose were 98.2 ng.hr/mL (Martin et al., 2003c) and 165.0 ng.hr/mL (Martin et al., 2003b). The \( [\text{AUC}] \) observed in our study after administration of 40 mg dose was 204.16 ± 54.98 ng.hr/mL. This value was also not very different from those reported in the literature.

The values of \( [\text{AUC}] \) after administration of 40 mg dose of oral tablet were 176 ng.hr/mL (Martin et al., 2003b) and 255 ng.hr/mL (Olsson et al., 2002). The \( [\text{AUC}] \) value found in present study was 206.65 ± 55.27 ng.hr/mL, which is also in close conformity to other reported. None of the PK studies reported MRT or AUMC values. MRT is an important PK parameter giving an estimate of drug stay (residence) in the body. The value of MRT calculated in our study was 5.60 ± 0.44 hr. Only one study reported Vd of rosuva after 10 mg dose which was 21500 mL/kg (Deng et al., 2008), while observed in our study was 19377 mL/kg, although a bit smaller value, but is also close to the one reported.
Table 1: Pharmacokinetic parameters of rosuvastatin after administration of a single 40 mg oral dose of rosuvastatin tablet

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Mean</th>
<th>± SD</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>29.07</td>
<td>6.88</td>
<td>25.85, 32.29</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>3.0</td>
<td>0.46</td>
<td>2.79, 3.21</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>204.16</td>
<td>54.98</td>
<td>178.43, 229.89</td>
</tr>
<tr>
<td>C&lt;sub&gt;L/F&lt;/sub&gt; (ng/hr/mL)</td>
<td>206.65</td>
<td>55.27</td>
<td>180.78, 232.52</td>
</tr>
<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt; (mL/kg)</td>
<td>1159.64</td>
<td>343.99</td>
<td>998.65, 1320.63</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>5.60</td>
<td>0.44</td>
<td>5.40, 5.81</td>
</tr>
<tr>
<td>Vd (mL/kg)</td>
<td>19377.23</td>
<td>9114.29</td>
<td>15111.61, 23642.8</td>
</tr>
<tr>
<td>CL/F (mL/hr/kg)</td>
<td>3275.26</td>
<td>1072.87</td>
<td>2773.14, 3777.38</td>
</tr>
<tr>
<td>E Half-life (hr)</td>
<td>3.99</td>
<td>0.75</td>
<td>3.64, 4.34</td>
</tr>
<tr>
<td>A Half-life (hr)</td>
<td>0.68</td>
<td>0.20</td>
<td>0.59, 0.77</td>
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</table>

Table 2: Pharmacokinetic parameters of NDM-Rosuvastatin (metabolite) after administration of a single 40 mg oral dose of rosuvastatin tablet

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Mean</th>
<th>± SD</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>2.36</td>
<td>0.45</td>
<td>2.14, 2.57</td>
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<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>4.0</td>
<td>0</td>
<td>NA (constant)</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>8.72</td>
<td>0.92</td>
<td>8.29, 9.15</td>
</tr>
<tr>
<td>C&lt;sub&gt;L/F&lt;/sub&gt; (ng/hr/mL)</td>
<td>9.44</td>
<td>1.24</td>
<td>8.86, 10.02</td>
</tr>
<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt; (mL/kg)</td>
<td>42.52</td>
<td>7.55</td>
<td>38.99, 46.05</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>4.65</td>
<td>0.35</td>
<td>4.48, 4.81</td>
</tr>
<tr>
<td>Vd (mL/kg)</td>
<td>106399.22</td>
<td>22512.92</td>
<td>95862.85, 116935.59</td>
</tr>
<tr>
<td>CL/F (mL/hr/kg)</td>
<td>65279.10</td>
<td>15427.29</td>
<td>58058.91, 72499.30</td>
</tr>
<tr>
<td>E Half-life (hr)</td>
<td>1.18</td>
<td>0.41</td>
<td>0.99, 1.37</td>
</tr>
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</table>

Table 3: Correlation between various PK parameters of rosuvastatin after administration of 40 mg oral dose

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>T&lt;sub&gt;max&lt;/sub&gt;</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>C&lt;sub&gt;L/F&lt;/sub&gt;</th>
<th>Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax</td>
<td>-0.069</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>C&lt;sub&gt;L/F&lt;/sub&gt;</td>
<td>0.883</td>
<td>-0.026</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CL/F</td>
<td>0.887</td>
<td>-0.041</td>
<td>1.000</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Vd</td>
<td>-0.691</td>
<td>-0.071</td>
<td>-0.832</td>
<td>-0.822</td>
<td>0.767</td>
</tr>
</tbody>
</table>

Clearance values reported after 40 mg dose was 11900 mL/hr (Martin et al., 2003b). It is obvious from the other reported data that there is large variation in the values of CL. Similarly, some researchers reported CL as a whole, while some reported CL on per kg body weight basis. We also reported the CL/hr/kg which is the more authentic and gives an accurate estimate of total clearance. The value of CL observed in our study was 3275.26 ± 1072.87 mL/hr/kg. Our observed clearance value was a little higher on per Kg basis than other reported values representing a bit quicker elimination in Pakistani population.

The reported elimination half-life (e-t<sub>1/2</sub>) value in other PK studies was 19.0 hr after 40 mg oral dose. The value of e-t<sub>1/2</sub> observed in our study was 3.99 ± 0.75 hr, which is much lower than those reported in other studies. This lower value of (e-t<sub>1/2</sub>) may be due to high rate of elimination leading to increased clearance rate thus making the half life shorter in Pakistani population. Another reason for the smaller e-half-life might be the sampling times (i.e., from 0 to 24 hrs) in our study, whereas other reported sampling up to 72 and 96 hrs. No PK study on rosuva has been performed up till now in Pakistani populations. As this drug is not used in acute emergency situations, therefore, a single dose (OD) will be sufficient for treating hyperlipidemia as recommended by FDA. However, if needed (in situations where the desired lipid profile is not achieved after prolong use), two times daily dosing (BD) may also be an option in Pakistani population only.
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The correlation between various PK parameters of rosuva calculated by Pearson correlation test is shown in table 3. The good correlation was observed between AUC and Cmax while good negative correlation was observed between CL/F, Vd, AUC and Cmax. While CL and Vd showed positive correlation.

The Cmax of NDM-rosuva reported by other researchers after administration of 10 mg and 80 mg oral dose of rosuva were 0.345 ng/mL and 7.2 ng/mL, respectively. No PK study of NDM-rosuva had been performed with 40 mg dose however, like rosuva, it showed proportional increase in plasma samples over the dose range of 10 – 80 mg. The tmax value for NDM-rosuva observed in our study was 4.0 hr, whereas reported in other studies was 4.33 hr (Busti et al., 2008) and 3.0 hr (Schneck et al., 2004). Therefore, this value is also similar to those reported in the literature.

The [AUC]0-8 hr reported by other researchers at the dose of 10 and 80 mg were 3.07 ng.hr/mL (Busti et al., 2008) and 50.2 ng.hr/mL (Schneck et al., 2004), respectively, whereas values calculated in the present study is 8.719 ng.hr/mL, which is relatively small and the reason may be that NDM-rosuva was not quantifiable in our study after 8 hr while it has been reported to be 12 and 24 hr following drug administration.

Our observed [AUC]0-24 hr value (mean ± SD) for NDM-rosuva was 9.44 ± 1.24 ng.hr/mL, whereas other studies didn’t report the value of [AUC]0-24 hr. Furthermore, no other study incorporated determination of clearance or Vd of NDM-rosuva therefore; relatively a small e-half-life of the NDM-rosuva in our study may be due to an enhanced clearance rate in Pakistani population.

Majority of PK studies of rosuva by other researchers determined only few PK parameters for NDM-rosuva such as Cmax, tmax, AUC and t1/2 whereas we reported additional PK parameters as well as AUC, AUMC, MRT and Vd in order to properly elucidate the PK profile of NDM-rosuva in Pakistani population. This PK study of rosuva and NDM-rosuva performed in local population presented somewhat similar PK profile as reported in other populations except Chinese population (Li et al., 2007).

Recent studies have demonstrated that polymorphism in the genetic makeup of transporters involved in rosuvastatin disposition greatly affect its pharmacokinetics. A PK evaluation study of rosuva in Finnish population (people of Finland) possessing polymorphism in ABCG2 transporter (ATP binding cassette G2-protein transporter also called BCRP) showed that the Cmax and [AUC]0-24 hr values of rosuva were higher in genotype C.421AA group by 108% and 100%, respectively, than genotype C.421CA and by 131% and 144% than genotype C.421CC, respectively (Keskitalo et al., 2009a).

These results were also in accordance to a study in Chinese population assessing the effect of BCRP 421 C > A (ABCG2) polymorphism over the PK of Rosuva demonstrating almost similar findings (Zhang et al., 2006). ABCG2 is the efflux transporter having role in rosuva absorption and hepatic uptake, therefore, polymorphism in genes encoding this transporter disrupts the plasma exposure of rosuva. The effect of single nucleotide polymorphism (SNP) in SLCO1B1 also known as OATP1B1 transporter (involved in rosuva’s hepatic uptake) over PK of rosuva has also been evaluated in Finnish population (Pasanen et al., 2007). The Cmax and [AUC]0-24 hr values of rosuva were greater in SLCO1B1 genotype C.521CC subjects by 65% and 79%, respectively than subjects with genotype C.521TT (Pasanen et al., 2007). These differences in transporter’s genetic makeup may account for the variability in PK of rosuva among different populations it is also evidenced by a study representing much higher concentrations and plasma exposure of rosuva in Chinese as compared with Asian Indians, Malay and white population (Lee et al., 2005).

However, a study evaluating the effect of genetic polymorphism in ABCB1 transporter over the PK of rosuva in white people indicated a non significant difference in the PK parameters between various haplotypes of ABCB1 (Keskitalo et al., 2009b).

The variations in the PK profile of rosuva among different studies reported in the literature and in this study may be attributed to transporters polymorphism. Although, the metabolism of rosuva occurs mainly by CYP2C9 and this enzyme possess greater genetic polymorphism, but the very little metabolism of rosuva (~10%) makes the effect of this polymorphism over the PK of rosuva negligible (Zhang et al., 2006), therefore, none of the PK studies of rosuva emphasized the genetic variations in the metabolizing enzymes and focused mainly on transporters polymorphism.

CONCLUSION

Variation in the pharmacokinetics of rosuva exists among different population over a dose range of 10-80 mg. The pharmacokinetics of rosuva in Pakistani male healthy volunteers determined with a single oral dose of 40 mg showed somewhat similar pattern to those reported in other population. Hence, optimal cholesterol lowering effect with the recommended dose and dosing schedule is also anticipated in Pakistani population.
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