Multiple dose of liquid antacid enhance simvastatin bioavailability in Malaysian male volunteers

Khaled M Al Akhali, Sirajudeen S Alavudeen

Department of Clinical Pharmacy, College of Pharmacy, King Khalid University, Abha, Kingdom of Saudi Arabia

The effect of a liquid antacid on the oral bioavailability of simvastatin 40 mg tablet was evaluated in 9 healthy Malaysian male volunteers in a randomized, single dose, two-way crossover study. The drug was administered following an overnight fast or a liquid antacid. The plasma concentration of simvastatin was determined by using a validated HPLC-MS-MS method. An effect of liquid antacid on the bioavailability was indicated 95% increase in the AUC of simvastatin with antacid state comparing to fasting state. The study was concluded that liquid antacid had effect on the increasing pH of gastrointestinal tract which leads to increasing the lactone form of simvastatin stability and improve the dissolution of the drug by increasing gastric residence time. This study revealed that simvastatin is pH-dependent.

Key words: Liquid antacid, fasting, simvastatin bioavailability

INTRODUCTION

Antacids are consumed in large quantities by patients with gastrointestinal disease. Although generally considered free of serious side effects, these drugs can potentially interact with other administered drugs, affecting the absorption and pharmacologic effectiveness of these other agents. Antacid products are widely used for the purpose of neutralizing gastric contents and elevating the pH of gastric contents.[1] It is known that change in the pH of gastrointestinal tract affects the absorbability of the ionized compounds, and is also known from animal data and, theoretically, in humans certain gel antacids and ion exchange resins might inhibit the absorption of other drugs. This type of interaction would theoretically be as much due to adsorption of the drug molecule on the physical system of the offending agent as much as to pH change. However, the data from animal studies showed that there is reduction in the plasma concentration of certain drugs along with antacid administration.[2-4] Additionally, the plasma concentrations of some drugs in animals were not affected by antacid administration.[4] Some of the human studies showed the reduction in plasma concentration of some drugs by administration of antacids[5-8] and some did not.[9-12] Based on the previous studies conducted in humans,[13-15] the absorption of drugs increased with antacid than with water.

Simvastatin, a lactone analog of lovastatin, used in the treatment of hypercholesterolemia lowers the plasma cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase.[16] The in vitro hydrolysis of lactone ring produces the hydroxyl acid, which is the active form of this drug.[17-19] The bioavailability of simvastatin given with antacid is unknown. The aim of the current study was to compare the rate and extent of absorption of single oral dose of 40 mg simvastatin (Zocor,[8] MSD) with fasting and antacid.

MATERIALS AND METHODS

Subjects and study design

Nine healthy, nonsmoking, Malaysian male volunteers participated in this study. The age of the healthy male participants, were between the age group of 22 and 49 years. The study protocol of administration of oral single dose of 40 mg simvastatin following the guidelines.
Pharmacokinetic analysis

The pharmacokinetics of simvastatin was characterized by peak concentration in serum (C_{\text{max}}), concentration peak time (T_{\text{max}}), elimination rate K_{\text{e}}, elimination half-life (t_{\frac{1}{2}}), and areas under the drug serum concentration-time curve up to 24 hours (AUC_{0-24}).

Statistical analysis

The data are expressed as mean values ± SD. Data were analyzed by Student’s t-test comparing the fasting and antacid conditions of each volunteer. In the case of T_{\text{max}}, Wilcoxon test was used. The statistical program SPSS for Windows version 11.5 will be used for the analysis. Differences were considered statistically significant when P < 0.05.

RESULTS

All the nine volunteers completed the study. A randomized, open-labeled, crossover design was used in this study. No adverse effects were observed during the study. The baseline characteristics of nine volunteers are shown in Table 1. The mean plasma of 40 mg simvastatin tablet concentration versus time profiles of volunteers after dosing with fasting and antacid states are shown in Figure 1.

The kinetic data for antacid and non-antacid conditions in plasma are given in Table 2. For both conditions (antacid and non-antacid), the inter individual variation was considerable with respect to peak concentrations and AUC_{0-24} values. However, co-administration of simvastatin with multiple dose of antacid (magnesia and alumina hydroxy mixture) (100 mL) produced higher AUC_{0-24} values than when the simvastatin was given with non-antacid. For AUC_{0-24} values ranged from 6.20 to 15.86 ng/mL·hr in non-antacid state and from 11.75 to 38.04 ng/mL·hr in antacid state. In each volunteer, the AUC_{0-24} was larger when simvastatin was taken together with the antacid than when simvastatin was given with non-antacid, except one volunteer the AUC_{0-24} was equal when simvastatin was given in both conditions. However, when

Sample analysis

Serum samples containing simvastatin were quantified by liquid chromatography tandem mass spectrometry (LC-MS-MS). The simvastatin was extracted from serum using ethyl acetate and hexane (90/10%, v/v) by using lovastatin as internal standard. The solutes were separated on a C_{18} column with mobile phase consisting of mixture of acetonitrile and 3 mM formic acid (75/25%, v/v) at flow rate 500 μL/min. For quantitation in the selective reaction monitoring (SRM) in positive ion mode, the daughter ions m/z 325 for simvastatin and m/z 285 for lovastatin were used. Parent ions in positive ion mode were m/z 441.3 for simvastatin and m/z 405.1 for lovastatin. The lower limit of quantitation of 0.25 ng/mL was achieved. The within-day coefficient of variations was less than 14.00% and the accuracies were between 90.00 and 109.33%. The day-to-day coefficients of variation were less than 10.00% and accuracies were between 97.70 and 106.60%.

### Table 1: Baseline characteristics of nine healthy volunteers

<table>
<thead>
<tr>
<th>Volunteer</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Body mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>49</td>
<td>58</td>
<td>163</td>
<td>21.8</td>
</tr>
<tr>
<td>V2</td>
<td>40</td>
<td>55</td>
<td>165</td>
<td>20.2</td>
</tr>
<tr>
<td>V3</td>
<td>22</td>
<td>67</td>
<td>169</td>
<td>23.5</td>
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<tr>
<td>V4</td>
<td>33</td>
<td>70</td>
<td>162</td>
<td>26.7</td>
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<tr>
<td>V5</td>
<td>24</td>
<td>85</td>
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<td>30.5</td>
</tr>
<tr>
<td>V6</td>
<td>23</td>
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<td>V8</td>
<td>31</td>
<td>78</td>
<td>179</td>
<td>24.3</td>
</tr>
<tr>
<td>V9</td>
<td>34</td>
<td>70</td>
<td>163</td>
<td>26.4</td>
</tr>
<tr>
<td>Mean</td>
<td>30.89</td>
<td>68.22</td>
<td>167.56</td>
<td>24.31</td>
</tr>
<tr>
<td>±SD</td>
<td>9.31</td>
<td>9.24</td>
<td>5.29</td>
<td>3.12</td>
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</tbody>
</table>

SD: Standard deviation
taking simvastatin with antacid, the mean (± SD) AUC\textsubscript{0-24} of the simvastatin increased from 10.90 ± 3.21 (fasting state) to 20 ± 9.57 ng/mL\textsuperscript{-1}hr (P < 0.05) the AUC\textsubscript{0-24} increased with antacid 95% higher than simvastatin given without antacid.

The peak concentrations ranged from 0.93 to 4.96 ng/mL in non-antacid and from 1.72 to 5.84 ng/mL in antacid state. The mean (± SD) C\textsubscript{max} of the simvastatin was increased from 2.61 ± 1.42 in non-antacid to 3.30 ± 1.53 ng/mL in antacid state. The difference in this mean between antacid and non-antacid conditions just failed to reach significance at the 0.05 level (P > 0.05).

Co-administration of simvastatin with multiple dose of antacid (magnesia and alumina hydroxy mixture) (100 mL) produced higher effect on the T\textsubscript{max}. The mean observed T\textsubscript{max} for simvastatin with antacid was considerable and significantly higher than when simvastatin was taken without antacid. However, antacid intake delayed the absorption of simvastatin, which is reflected both by a delay in T\textsubscript{max} as well as a more prolonged lag time prior to the appearance of measurable concentrations of simvastatin in blood. The mean (± SD) T\textsubscript{max} of the simvastatin increased from 1.33 hr ± 0.71 (empty stomach with water) to 3.06 hr ± 1.33 (P < 0.05, Wilcoxon matched-pair signed-rank test). The increase with antacid was more than 100% higher than fasting state.

The half-life obtained in this study was not influenced by antacid. However, mean observed t\textsubscript{1/2} determined for simvastatin shows no significant difference between antacid and non-antacid states: 3.16 ± 1.68 and 4.38 ± 1.43 hours, respectively (P > 0.05).

Table 2: Pharmacokinetic parameters of simvastatin in nine volunteers after 40 mg oral simvastatin in fasting and with antacid conditions

<table>
<thead>
<tr>
<th>Subject</th>
<th>AUC\textsubscript{0-24} ng.mL\textsuperscript{-1}.hr</th>
<th>C\textsubscript{max} (ng/mL)</th>
<th>T\textsubscript{max} (hr)</th>
<th>t\textsubscript{1/2} (hr)</th>
<th>K\textsubscript{e} (1/hr)</th>
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<td></td>
<td>F</td>
<td>A</td>
<td>F</td>
<td>A</td>
<td>F</td>
</tr>
<tr>
<td>1</td>
<td>15.86</td>
<td>30.73</td>
<td>2.13</td>
<td>3.63</td>
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</tr>
<tr>
<td>2</td>
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<td>37.08</td>
<td>1.23</td>
<td>5.42</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>8.95</td>
<td>11.90</td>
<td>0.93</td>
<td>1.72</td>
<td>3.00</td>
</tr>
<tr>
<td>4</td>
<td>12.70</td>
<td>12.10</td>
<td>3.90</td>
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</tr>
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<td>1.90</td>
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</tr>
<tr>
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<td>6.97</td>
<td>11.75</td>
<td>1.86</td>
<td>1.77</td>
<td>1.00</td>
</tr>
<tr>
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<td>10.40</td>
<td>17.30</td>
<td>2.33</td>
<td>2.01</td>
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<tr>
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<td>14.40</td>
<td>28.70</td>
<td>4.28</td>
<td>3.42</td>
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</tr>
<tr>
<td>9</td>
<td>11.70</td>
<td>15.98</td>
<td>4.96</td>
<td>5.84</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean</td>
<td>10.90</td>
<td>20.00</td>
<td>2.61</td>
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<td>1.33</td>
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<tr>
<td>±SD</td>
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<td>9.57</td>
<td>1.42</td>
<td>1.53</td>
<td>0.71</td>
</tr>
<tr>
<td>P</td>
<td>0.008</td>
<td>0.274</td>
<td>0.016</td>
<td>0.116</td>
<td>0.012</td>
</tr>
</tbody>
</table>

F: Fasting, A: Antacid
The mean observed $K_e$ (elimination rate) determined for simvastatin did not show any significant difference between non-antacid and antacid states: 0.29 ± 0.16 and 0.18 ± 0.09/hour, respectively ($P > 0.05$).

**DISCUSSION**

Gastrointestinal (GI) fluid pH, which varies considerably along the length of the gastrointestinal tract (GIT), may have influence on drug absorption. A drug dosage form is initially exposed to the acidic pH in normal stomach (pH 1-3) and an abrupt increase in pH, once it enters the small intestine as a result of pancreatic secretion. The pH of intestinal fluid ranges from 5-6 in the duodenum to 7-8 in the proximal jejunum and approaches a pH of about 8 in the large intestine. Among the factors affecting the pH of GI fluid are food ingestion, type of diet, stress, general health of the subject and the presence of local disease conditions along the tract.[20]

The stability of a drug in gastrointestinal fluids can be assessed by simulated gastric and intestinal media or by obtaining gastrointestinal fluids from humans or animals. Poor bioavailability results if degradation is extensive. This effect of gastric pH on digoxin has been reported by Gault et al. (1980)[21] and Gault et al. (1981).[22] When a drug is unstable in gastric fluids, rapid dissolution may reduce bioavailability.[21,22]

In addition, the half-life of degradation of penicillin G is less than 1 min at pH 1.0 and about 9 min at pH 2.0. The degradation rate of penicillin G decreases sharply with increasing pH, and the drug is stable in the small intestine. Therefore, chemical inactivation in the stomach is partially responsible for the relatively low bioavailability of penicillin G after oral administration.[25]

Graphical representation shows the increase in area under the curve of simvastatin in plasma after the administration of multiple doses of antacid, suggesting that there was an increase in the total amount of simvastatin absorbed. In addition, the shape of the plasma level curve changed so that the peak was higher and occurred later than that of the fasting state. The mean observed $T_{\text{max}}$ for simvastatin with antacid is considerable and significantly higher than when simvastatin is taken on empty stomach with water. The longer gastric residence time of the drug is offset by the rise in the pH of gastrointestinal tract.[18]

Most drugs are either weak bases or weak acids. They are usually better absorbed through the lipid membranes when they are in more lipid soluble forms, i.e unionized. According to the pH partition theory, raising the pH should decrease the rate of absorption of weakly acidic drug but increase that of weakly basic drugs. However, the rate of absorption of acidic drugs such as sulfonamides and aspirin is actually increased by the simultaneous ingestion of antacid.[26]

According to the pH partition theory, raising the pH should decrease the rate of absorption of weakly acidic drug but increase that of weakly basic drugs. Some studies showed that the absorption of a drug when taken with antacid has been found to be lower than when the drug was taken alone or it might have no effect,[5-8,9-12]

The critical pH for the instability of simvastatin in vitro study by Kaufman (1990)[18] was about 2. Since lactone hydrolysis reactions are strongly accelerated by general acid catalysis,[19] it is anticipated that conversion of lactone into its hydroxyl acid may occur in the strongly acidic gastric environment. Obviously, the desirable tissue selectivity of the lactone form is not realized if hydrolytic conversion in the GIT occurs rapidly relative to lactone absorption. In addition, in vitro study showed that the lactone form in aqueous solution is susceptible to pH dependent hydrolysis at pH 2.[18] The maximum stability of lactone form is at pH 5 and no degradation of the lactone in 24 hours at pH 5 was observed.[19]

In addition, the study conducted by Garrett and Won (1971),[17] explains in vitro the stability of lactone form in gastric fluid as a function of pH. Moreover, it was concluded that the inter conversion of lactone and acid can serve as background for biopharmaceutical and pharmacokinetic studies of canrenone (lactone) and canrenone acid and as a basis for optimal design of appropriate dosage forms.

Our study in vivo is in-agreement with previous studies in vitro conducted by Garrett and Won et al. (1971),[17] Kaufman et al. (1990)[18] and Serajuddin et al. (1991).[19] In this study, the observation of much higher plasma levels of the simvastatin after ingestion with liquid antacid was found. This effect may be resulted by increasing the pH of gastrointestinal tract caused by liquid antacid, which leads to increase in the stability of lactone form of simvastatin in GIT and improving dissolution of the drug by increasing gastric residence time.

The mechanism of ester hydrolysis reaction has been extensively studied and can be applied to the hydrolysis of the lactone form.[18]

In this current study, the absolute bioavailability with antacid is higher than non-antacid conditions. There is a 95% increase in AUC with antacid versus non-antacid conditions. Also, the $C_{\text{max}}$ (after a 40 mg simvastatin tablet) is greater with antacid than with non-antacid and the $T_{\text{max}}$ is also longer. The results in current study display similar pharmacokinetic profile in the presence of antacid as conducted by previous studies Sommers et al. (1984);[14] Hughes et al. (1989).[15] These results could be very useful in protecting this simvastatin pro-drug from hydrolysis by gastric acid secretion. This study revealed that simvastatin is pH-dependent.

Additionally, Mauro (1993)[27] reported the results from studies performed in the United Stated and Europe. He states...
that the daily doses of simvastatin of 10 and 40 mg reduce total plasma cholesterol by 20 and 30%, respectively. While, studies performed with Japanese patients indicate that an approximately 20% reduction in cholesterol occurs with a 5 mg daily dose of simvastatin. This difference in effect has been attributed to differences in genetic and physical factors.[29] But, this effect was explained in more detail by Russell et al., (1993)[28]. He states that the incidence of achlorhydracia appears to be much higher in Japanese people than European and American people. In addition, in Japanese people a 60% incidence of elevated gastric pH even in the 55 to 59 age bracket, whereas most of the European and American studies report incidences well below 5% in a similar age range.

Finally, this current study recommends the formulation of simvastatin with an antacid to minimize the instability of the former drug in gastric acid. To improve simvastatin bioavailability, it is necessary to find a protective formulation to decrease gastric acid attack in the stomach.

Furthermore, simvastatin acid tends to be eliminated in feces, secondary to biliary secretion.[28] Approximately 60% was recovered in feces, which represented unabsorbed drug and biliary excretion of simvastatin acid.[28,30] The current study recommends further studies on the excretion of simvastatin acid in feces. This effect may be due to biliary excretion or may be due to simvastatin hydrolysis in the gastrointestinal tract thereby increasing the rate of release of simvastatin acid, which cannot be absorbed by the intestinal wall and then excreted in feces.

**CONCLUSION**

The study can conclude that liquid antacid can enhance the absorption of simvastatin due to the stability of lactone form by increasing the pH of gastrointestinal tract.

**REFERENCES**