Influence of seven beverages on salicylate disposition in humans

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SUMMARY

Objective: Aspirin administered orally is one of most widely self-prescribed drugs to treat headaches or other pains. The aim of this study was to evaluate whether the influence of different beverages may be used to help in the ingestion of an aspirin tablet on the pharmacokinetic parameters of this drug. Method: This study was undertaken in five healthy volunteers. Seven beverages were tested: water, tea, coffee, orange juice, milk, beer and 40° distilled alcohol. After plasma extraction, aspirin and salicylic acid were measured by HPLC with UV detection. The main pharmacokinetic parameters were determined by the compartmental method and drug disposition profiles by the Wagner–Nelson modified method. Results: Elimination was not modified by any of the beverages but absorption was affected. Two opposing effects were observed: 40° alcohol seemed to increase AUC and Cmax. Milk and beer seemed to decrease these parameters. With 40° alcohol and tea, the amount absorbed and the disposition rate were higher. For milk and orange juice, the amount absorbed was lower and the disposition rate was unaffected. For beer, both the amount absorbed and the disposition rate increased. For coffee, both the amount absorbed and disposition rate were not significantly modified.

Conclusion: The bioavailability of salicylates on the healthy volunteers in this study was significantly affected by concomitant administration of 40° alcohol (spirit), beer and milk. The beverages seem to interfere with aspirin absorption and the drug disposition profile was modified.

Keywords: aspirin, beverages, interactions, pharmacokinetic, salicylic acid, Wagner–Nelson modified method

INTRODUCTION

Interactions between beverages and drugs can affect the efficacy of drug treatment and their side-effect profiles. These interactions can, in some cases, be used to improve drug absorption or to minimize adverse effects. Nevertheless, little has been published on this subject. Alcohol (1), milk (2) and, more recently, grapefruit juice (3–5) have been studied in this context, but these studies were carried out with drugs with a limited therapeutic range. In many healthcare systems, self-medication by the patient has increased greatly. Aspirin taken orally is one of most widely self-prescribed drugs for sudden headaches or other pains. Unless prior dissolution in water is required, as is the case with effervescent and soluble tablets or powders, the patient will usually swallow his aspirin tablet with a glass of water. If water is not available, any other available beverages may be used.

The aim of this study was to evaluate this potential effect of several common beverages on aspirin pharmacokinetics. Classical pharmacokinetic parameters were determined, and the drug disposition profile was calculated by the Wagner–Nelson modified method.

MATERIALS AND METHODS

Materials

Methanol was obtained from Flandre-Chimie (Villeneuve d’Ascq, France), potassium dihydrogenophosphate, trichloracetic acid and orthophosphoric acid from Prolabo (Paris, France). Aspirin and salicylic acid were purchased from Merck.
The drug administered was Aspirine du Rhone® (Rhone-Poulenc Rorer, France). This drug is an uncoated tablet containing 500 mg of aspirin.

**Clinical trial**

This study included five healthy volunteers (four females and one male) aged 23–45, weighing between 45 and 95 kg. None of the volunteers took any medication containing aspirin during the week before the beginning of the trial.

Seven beverages were tested sequentially by each subject in random order: water, tea, coffee, orange juice, milk, beer and 40° alcohol (whisky, rum or vodka). On the morning of the trial, fasted subjects ingested an aspirin tablet with one of these beverages (200 mL, except for 40° alcohol beverage: 50 mL), which were absorbed at different temperatures: coffee, tea and milk at 50°C; beer, orange juice at 10°C and water at room temperature. Fourteen blood samples (about 0.5 mL) were drawn from the fingertip at regular intervals over 24 h: 20, 40, 60 min in the first hour and then at 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 13 and 24 h. A wash-out of one week was included between each trial.

The samples were centrifuged (Biofuge 13, Heraeus) at 10000 r.p.m. (3000 g) for 5 min in heparinized Eppendorf tubes. The plasma was then collected.

**Analytical procedure**

*Extraction procedure.* The plasma levels of the main salicylate derivatives, aspirin and salicylic acid, were evaluated after precipitation of plasma proteins by adding 400 μL aqueous trichloracetic acid solution (6% w/v) to 400 μL plasma. After centrifugation, under the same conditions as described above, the supernatant was directly injected into the HPLC chromatograph.

*Chromatographic procedure.* The chromatographic system used was composed of a Shimadzu LC-6A pump (Touzard et Matignon, France), a Shimadzu SPD 2A scanning ultraviolet spectrophotometer (Touzard et Matignon) at 286 nm, and a Merck D-2000 integrator. The injection was carried out with a 20 μL Rheodyne loop.

The assessments of aspirin and salicylic acid concentrations were performed after chromatographic separation by inverse phase partition (Lichrosorb RP 18 column, 250 mm × 4.6 mm, 10 mm). The mobile phase was composed of potassium dihydrogenophosphate 0.01 m, methanol (66, 34 v/v) buffered at pH 3 obtained with 10% orthophosphoric acid. Phase flow was regulated at 1.8 mL/min. Linearity was checked between 1.25 and 25 μg/mL for each analyte (aspirin and salicylic acid). The detection limit was established at 1 μg/mL for both analytes.

**Parameter calculations**

The following pharmacokinetic parameters were calculated: maximum concentration (C max,cal), time of maximum absorption (T max,cal), absorption and elimination half-lives (T 1/2abs and T 1/2el), lag time (T lag), area under the curve (AUC). The drug disposition profiles were determined by the Wagner–Nelson method modified as follows:

\[ A\%_t = \frac{100}{k_e \times AUC_{\infty}} \times (C_t + k_e \times AUC_t) \]

where A% = percent of drug available, AUC = total area under the curve, AUCt = partial area under the curve at time t, Ct = plasma level at time t and k_e = elimination constant.

The rate of disposition dA%/dt was calculated between time n-1 and time n+1 from percentage of available drug as follows:

\[ \frac{dA\%}{dt} = \frac{A_{n+1} - A_{n-1}}{t_{n+1} - t_{n-1}} \]

All the calculations were made with Kinetica 2.0 Software (Innaphase, France).

**Statistical tests**

The drug disposition profile comparison was carried out using the Moore test (6). This test was divided into a two-step process as follows: estimation of the difference factor f_1 and evaluation of the similarity factor f_2. To be able to conclude that a similarity exists between two curves, f_2 must be >50% and the greatest f_1 <10%.

For comparison of the pharmacokinetic parameters, the paired Student test was used. The level of significance was set at 5%.
Table 1. In vivo pharmacokinetic parameters calculated after administration of 500 mg aspirin tablets, to five fasted volunteers, in the morning. Values presented in bold characters represent values showing a significant difference compared to water values (reference). Values show mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>$T_{lag}$</th>
<th>AUC</th>
<th>MRT</th>
<th>$C_{max;calc}$</th>
<th>$T_{max;calc}$</th>
<th>$T_{1/2;K_a}$</th>
<th>$T_{abs}$</th>
<th>$T_{1/2;Kel}$</th>
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<tr>
<td>Water</td>
<td>0.16</td>
<td>241.88</td>
<td>3.50</td>
<td>38.16</td>
<td>1.98</td>
<td>0.85</td>
<td>4.23</td>
<td>2.37</td>
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<td>Orange juice</td>
<td>0.16</td>
<td>79.59</td>
<td>0.93</td>
<td>6.34</td>
<td>0.87</td>
<td>0.53</td>
<td>2.63</td>
<td>0.61</td>
</tr>
<tr>
<td>Milk</td>
<td>0.58</td>
<td>264.38</td>
<td>3.48</td>
<td>37.39</td>
<td>2.60</td>
<td>1.15</td>
<td>5.75</td>
<td>2.71</td>
</tr>
<tr>
<td>Alcohol 40°</td>
<td>0.09</td>
<td>267.32</td>
<td>3.66</td>
<td>42.46</td>
<td>1.48</td>
<td>1.10</td>
<td>5.48</td>
<td>2.64</td>
</tr>
<tr>
<td>Milk</td>
<td>0.71</td>
<td>170.34</td>
<td>2.42</td>
<td>27.47</td>
<td>2.70</td>
<td>1.13</td>
<td>5.65</td>
<td>2.18</td>
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<td>Coffee</td>
<td>0.46</td>
<td>38.14</td>
<td>1.65</td>
<td>2.62</td>
<td>0.83</td>
<td>0.67</td>
<td>3.34</td>
<td>0.89</td>
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<td>267.18</td>
<td>3.87</td>
<td>39.62</td>
<td>2.06</td>
<td>0.79</td>
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<td>135.36</td>
<td>1.22</td>
<td>13.18</td>
<td>0.60</td>
<td>0.36</td>
<td>1.81</td>
<td>0.74</td>
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<tr>
<td>Beer</td>
<td>0.19</td>
<td>249.68</td>
<td>4.14</td>
<td>40.18</td>
<td>1.46</td>
<td>0.62</td>
<td>3.10</td>
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<td>104.95</td>
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<td>13.53</td>
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<td>2.00</td>
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Fig. 1. Profiles of mean salicylate serum levels obtained after administration of 500 mg aspirin tablet with different beverages (dotted line) compared to water profile (continuous line).
RESULTS

The mean serum levels vs. time profiles of salicylates (acid salicylic and aspirin) are presented in Fig. 1. Significant interbeverage variation was observed. Statistical analysis of serum level profiles showed a significant influence for three beverages: beer, milk and 40° alcohol. The main modifications were observed in three parameters: $T_{lag}$, $C_{max\text{cal}}$ and AUC (Table 1), whereas elimination was not modified. The elimination half-life remained constant (Table 1). In fact, two opposing effects were observed: 40° alcohol seemed to increase bioavailability (AUC and $C_{max\text{cal}}$ increased), milk and beer seemed to decrease bioavailability (AUC and $C_{max\text{cal}}$ decreased), and milk also seemed to increase lag time (Table 1).

The analysis of salicylate disposition profiles was performed using the Wagner–Nelson modified method. The salicylate disposition amount profiles and the disposition rates obtained during the first 4 h are displayed in Figs 2 and 3. The statistical test (Table 2) showed that the amount of salicylate absorbed was influenced by the beverage taken concomittantly. For 40° alcohol and tea, drug disposition and the disposition rates were significantly increased. For milk and orange juice, drug

\[\text{Fig. 2. Profiles of mean salicylate amount available after administration of 500 mg aspirin tablet, using the Wagner–Nelson modified method, with different beverages (dotted line) compared to water profile (continuous line).}\]
Disposition was significantly decreased and the disposition rate was constant and superior to that observed with water. For beer, both drug disposition and the initial disposition rate were significantly increased. For coffee, drug disposition and disposition rate were not significantly modified (Figs 2 and 3; Table 1).

**DISCUSSION**

Drug disposition, i.e. drug transfer from tablet to the general blood circulation, requires: (a) disintegration, initial rupture of the tablet, (b) disintegration or separation of the tablet fragments into finer particles, (c) dissolution of the drug in the gastrointestinal fluids, (d) absorption through gastrointestinal barrier cells and (e) the first pass effect or initial metabolism by intestinal and liver cells. These processes mainly occur successively but may also occur concurrently. In the present study, alteration in the drug disposition profile was most likely due to an effect on the disintegration–dissolution profile.

40°C alcohol and tea increased the drug’s bioavailability (Figs 1b and e, Table 1) and its rate of elimination (Figs 2b and e, 3b and e). For beverages with a high alcoholic content, several reasons can account for this effect. The first effect is

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**Fig. 3.** Profiles of mean salicylate disposition rates obtained after administration of 500 mg aspirin tablets, with different beverages (dotted line) compared to water profile (continuous line).
an increase in the dissolution rate because of better aspirin solubility in the gastrointestinal fluids (7, 8). The second effect is the capacity of alcohol to block gastric acid production by direct action on the mucosal cells (9). The third effect is irritation of the mucosa. When the mucosal barrier is breached, exfoliation of the cells occurs followed by damage to the capillaries. The consequence is an increase in absorption rate (7–10). On the other hand, alcohol may stimulate pyloric opening to decrease aspirin content in the stomach, and hence more rapid absorption in the small intestine (9).

The result observed with tea could be due to a temperature effect or to the pH of this beverage. A high temperature (50 °C) and alkaline pH (7–7) would be expected to increase the dissolution rate. Moreover, it is well known that alkalinity speeds up gastric emptying, which speeds up absorption of the dissolved drug through contact with a larger absorption surface. Tea contains caffeine (1–5%) (11), which is known to increase the absorption rate of aspirin (12) by increasing its solubility.

The effect of orange juice is more difficult to explain. Indeed, the AUC and the lag time were not significantly modified (Fig. 1a, Table 2). The profile of drug amount disposition is modified in comparison with water (Fig. 2a, Table 2), and the drug disposition rate is at first constant then in the second step, the rate increases (Fig. 3a). The constant rate in the first stage signifies that order of this reaction is zero. This may be due to the acidic pH of orange juice (2.5–3.5), which slows down gastric emptying (13). Orange juice is rich in polysaccharides (energy contents), which decreases gastric emptying considerably (14). In these conditions, aspirin solubility is low, with the boundary layer in contact with the solid surface containing a saturated solution of salicylates and hence a slow dissolution. With milk, bioavailability is decreased (Fig. 1c, Table 1) and drug disposition and its rate are lower (Figs 2c and 3c). The pH of milk (6.5) increases ionization. The ionized form cannot be absorbed by mucosa cells. Moreover, milk contains lipids and proteins that slow down gastric emptying for the same reason as polysaccharides (14), and so passage absorption is delayed, with a significant increase in lag time (Table 1). However, the decrease in bioavailability is probably due to the formation of insoluble calcium salicylates (13) (Table 1).

The results obtained with beer seem to be conflicting. Indeed, the AUC is decreased (Fig. 1f, Table 1), but drug disposition and the disposition rate are increased (Figs 2f and 3f). Beer is a complex mixture. The low alcohol content increases gastric acidity and then decreases dissolution (15). The presence of protein and glucose in beer can also slow down gastric emptying, but carbon dioxide and hypertonicity may speed up emptying (15). The result here is a speeding up of emptying because the lag time disappears. The lower AUC may be due to precipitation or complex-formation with a beer ingredient. Coffee seems to have no effect on the salicylate serum profile. This result conflicts with those of previous studies (12–16) and may be due to great interpatient variation and the small population sample size.

CONCLUSION

The bioavailability of aspirin in healthy volunteers is significantly affected by concomitant administration of 40° alcohol (spirit), beer and milk (Fig. 4). While the clinical implications are

| Table 2. Difference factor $f_1$ and similarity factor $f_2$ calculated for each curve |
|---------------------------------|-----|------|-----|
| Beverage           | $f_1$ | $f_2$ | Similarity |
| Orange juice       | 43:02 | 45:29 | No   |
| Alcohol 40°        | 64:01 | 36:70 | No   |
| Milk              | 80:80 | 31:65 | No   |
| Coffee            | 9:67  | 57:52 | Yes  |
| Tea               | 53:54 | 40:56 | No   |
| Beer              | 24:59 | 50:07 | No   |

probably modest, this study provides information for better advising patients on optimizing drug effects and highlights possible complications when treating patients with drugs that have narrower therapeutic ranges.

REFERENCES