Coffee Modify Pharmacokinetics of Acetaminophen

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Abstract

Aim: Acetaminophen (paracetamol) is commonly used as analgesic and antipyretic agent. This drug is taken together with coffee sometimes but effect of drinking coffee on pharmacokinetics of oral acetaminophen is not stated. So, to explore the interaction of coffee with paracetamol is considered to avoid toxicity.

Methods: To assess the influence of coffee on the pharmacokinetic of acetaminophen, a complete one way cross-over design study was done in fifteen normal healthy male volunteers in which each subject performed as its own control. Each subject received acetaminophen (500 mg) alone followed by acetaminophen with 1g and 3g of coffee containing 65 mg and 195 mg of caffeine at 2 weeks interval. Caffeine concentration in coffee was determined by high performance liquid chromatography method (HPLC) and serum acetaminophen concentration was assayed by spectrophotometry. Acetaminophen pharmacokinetic parameters were determined.

Results: There was an increase in acetaminophen rate and extent of absorption with coffee containing 65 mg of caffeine (P < 0.001) but decrease absorption rate with drinking coffee containing 195 mg of caffeine (P < 0.001), increase maximal plasma drug concentration (Cmax) and the elimination half-life (T1/2el) were prolonged after taking acetaminophen with coffee.

Conclusion: In this study, coffee may enhance the production of optimal therapeutic effect of and prolong duration of acetaminophen action. This synergistic action might be alteration of pharmacokinetics of acetaminophen by coffee. So, acetaminophen taken together with coffee containing 65 mg and 195 mg of caffeine (one to three cups of coffee) may produce a better therapeutics outcome.

Keywords: Acetaminophen; Coffee; Pharmacokinetic; Caffeine

Abbreviations

HPLC: High Performance Liquid Chromatography Method; Cmax: Maximal Plasma Drug Concentration; Tmax: Peak Concentration; T1/2ab: Absorption Half-Lives; T1/2el: Elimination Half-Life; AUC: Plasma Concentration-Time Curve

Introduction

Acetaminophen (Paracetamol; N-acetyl-P-aminophenol) is the known synthetic analgesic and antipyretic drug. It is a para-aminophenol derivative and the active metabolite of phenacetin. Clinically, it was first used in medicine as analgesic and antipyretic drug since 1893. Its use becomes extensive in 1949 after recognition as both acetanilide and phenacetin’s major active metabolite. Analgesic and antipyretic effects of acetaminophen do not differ significantly from those of acetylsalicylic acid (ASA) [1].

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Acetaminophen is usually administered as oral tablets but now available in the form of capsules, elixirs [2] and suppositories [3] under many brand names, either alone or combination with other drugs. It is useful for the relief of mild to moderate pain and is safe when used in appropriate dosage during a brief period of use. It is an over-the-counter (OTC) analgesic approved as the first OTC agent for migraine in the United States. There are several advantages of OTC drugs such as easy access, lower cost and fewer adverse effects. It is a drug of choice for the most migraine patients who treated their headaches with OTC medication in the United States [4].

Caffeine was first isolated and characterized in 1895 and used as an additive to analgesic. Caffeine contains in many beverages (coffee, tea and cola drinks). It has central nervous system (CNS) stimulant effect. It has potential for psychic dependence. Untoward effects common with high consumption (> 600 mg/day). Caffeine has been an additive in analgesic for many years. However, it has not been seriously investigated how caffeine produce analgesic adjuvant effects. The study in 1984 reported that caffeine reduced to approximately 40% of acetaminophen necessary for the same effect [5]. Clinical trials suggested that more than 65mg caffeine may be useful for the enhancement of analgesia [6].

Tukker., et al. [7] studied the influence of caffeine on the acetaminophen rate and extent of absorption by using a combination of 50 mg caffeine and 500 mg acetaminophen tablet. There was positive influence of caffeine on the absorption rate of acetaminophen but no influence on the acetaminophen extent of absorption. Castanede-Hernandez., et al. [8] investigated the acetaminophen pharmacokinetic effects when caffeine given as combination in female Wistar rats. Acetaminophen was administered at 316.2 mg/kg; with caffeine at 32 mg/kg. Acetaminophen pharmacokinetics was not altered by caffeine adding in rats. However, they found that analgesic effect was greater than that of acetaminophen alone.

There was superior reduction in pain in subjects taking acetaminophen (648 mg) with caffeine 65 mg and 130 mg than subject taking acetaminophen alone or caffeine alone. The pain was assessed by the profile of mood states (POMS) and visual analog (VA) pain scale using a 10 cm line with left end regarded as "no pain", right end regarded as "pain as bad as it could be", "mild, moderate, severe" written in sequences beneath the line. Regarding potential effects of caffeine on headache, three major hypotheses were reported. (1) Caffeine alone is analgesic that directly and independently reduces pain. (2) Indirectly reduces reported pain by caffeine due to improvement in mood. (3) Caffeine reduces caffeine withdrawal headache or migraine [9].

When acetaminophen and caffeine are given together, it may give rise to faster cure for a headache. Caffeine is a weak stimulant, which reduces headache by increasing a person’s wellbeing. The influence of caffeine (60 mg) on pharmacokinetic characteristic of acetaminophen (500 mg single dose) was studied in ten healthy volunteer men in complete cross-over design. Caffeine causes a highly significant increase (P < 0.01) in area under the plasma concentration-time curve (AUC) and area under the mean plasma concentration-time curve (AUMC), a significant increase (P < 0.05) in maximal plasma or serum concentration (Cmax), a significant decrease (P < 0.05) in clearance (Cl/F) of acetaminophen. So, amount of caffeine commonly containing in one cup of coffee can significantly potentiate the therapeutic potential of acetaminophen in man [10].

In contrast, Wojicicki., et al. [11] examined acetaminophen pharmacokinetics changes by caffeine in a crossover study in 9 healthy persons. Each person received either 1000 mg acetaminophen in tablets, or a combination of acetaminophen 1000 mg with caffeine100 mg. The combination of both lowered drug level significantly after upto 1.25hr, and significantly decreased in Cmax and AUC, as well as increased in time to reach Cmax (Tmax) and elimination half-life (T1/2).

The interactions of caffeine with acetylsalicylic acid and acetaminophen were studied in concern to analgesic, antipyretic and other properties in rats. The antinociceptive effect of acetaminophen was additively increased by caffeine with regard to heat-induced pain in the mouse, like aminophenazono as well as antipyretic effect of acetaminophen was additively increased by caffeine in rats [12].

Acetaminophen and caffeine combination has synergistic for analgesic effect. It may be pharmacodynamics or pharmacokinetics reasons. This study tried to find out if the reason is pharmacokinetic, how caffeine can alter the pharmacokinetic parameters (Cmax, Tmax, T1/2, AUC, etc.) of acetaminophen. The pharmacokinetic studies on acetaminophen with coffee will be useful for more effective treatment of acetaminophen.
Materials and Methods

A complete one way cross-over study design was employed. Subjects between 18 and 50 years of age men were included in this study. Subjects with a history of gastric pain, heart burn, palpitation, taking drugs which have effect on liver functions and chronic alcoholics were excluded for this study. Each subject receives acetaminophen alone; in combination with coffee containing caffeine 65mg and 195 mg, so that each subject performed as its own control. Each subject was given, one tablet of acetaminophen (500 mg) with 150 ml of water in fasting state. No food was allowed until 2 hours after giving the dose. And then, one tablet of acetaminophen (500 mg) with 150 ml of coffee 1g (containing 65 mg caffeine) and 150 ml of coffee 3 g (containing 195 mg caffeine) were taken by each subject at two weeks interval between the trials. 20 ml of blood just prior to dosing and 10 ml of blood at 0 min, 15 min, 30 min, 45 min, 1 hr, 2 hr, 4 hr, 8 hr and 24hr after dosing were corrected. The collected samples were centrifuged at 2000 rpm for 10 minutes and the separated serum samples stored at -20ºC until the time of assay.

The serum working standards containing 1.25, 2.5, 5, 10, 20, 40, 80 µg/ml of acetaminophen were prepared on each day of assay. The unknown samples were investigated as follows: 2.4 ml Tri-chloroacetic acid 5% was added to 0.6 ml of serum, mixed and centrifuge for 10 minutes. The supernatant 2 ml was removed with a micropipette and transferred to 10 ml test tube with rubber stopper. The tubes were sealed and placed for 20 minutes in boiling water bath. After removal, any condensation occurring at the top of the tube was dissolved inverting the tubes. After that, cool down to room temperature and 1 ml of 1% orthocresol solution was added and mixed in the tubes. This step was followed by addition of 2 ml of 4M ammonia solution. After mixing, the tubes were then retained in boiling water bath for an additional 5 minutes.

Then, absorbance was measured at 615 nm in spectrophotometer after cooling down to room temperature according to Miceli, et al [13].

Standard curve for acetaminophen was drawn by using standard (known concentrations) solutions. Pooled serum was used as blank solution. A standard curve was drawn daily by measuring the optical density of a series of different concentrations of acetaminophen in serum at the wavelength of 615 nm. Optical densities of different concentrations were plotted as shown in figure by using the least square method (Figure 1).

![Figure 1: Acetaminophen Standard concentration curve.](image-url)
Results and Discussion

Serum drug concentrations of acetaminophen of each subject at various times were obtained from reading the standard curve. The mean peak serum acetaminophen concentration with and without caffeine were shown in figure 2. Mean peak serum concentration achieved was 12.57 ± 0.78 (without coffee), 13.52 ± 0.71 (with coffee containing 65 mg caffeine) and 13.91 ± 0.70 (with coffee containing 195 mg caffeine). Mean peak serum concentration ($C_{\text{max}}$) of acetaminophen was increased by 7.6% and 10.6% with both doses of caffeine (65 mg and 195 mg). The difference in peak serum acetaminophen concentration were statistically significant (p < 0.05).

![Mean Peak Serum Concentration of Acetaminophen](image)

*Figure 2: Peak serum acetaminophen concentration.*

Times to reach the peak concentration ($T_{\text{max}}$) were 100 ± 16.93 minutes (without coffee), 56 ± 7.39 minutes (with coffee containing 65 mg caffeine) and 151 ± 17.85 minutes (with coffee containing 195 mg caffeine). The reduction in $T_{\text{max}}$ (quick $C_{\text{max}}$) was seen with 65 mg caffeine and increase in $T_{\text{max}}$ (delayed $C_{\text{max}}$) was seen with 195 mg caffeine and these findings were statistically significant (p < 0.05).

The mean time to reach minimal effective concentration (MEC) of acetaminophen was 69.6 ± 4.3 minutes when acetaminophen was given alone. This value was reduced significantly (p < 0.05) to 35.1 ± 1.2 minutes when acetaminophen was taken together with coffee containing 65 mg caffeine. When acetaminophen was taken together with coffee containing 195 mg caffeine, this value was increased to 78.6 ± 3.6 minutes which was not significant when compared to acetaminophen alone.

Mean absorption half-lives ($T_{1/2ab}$) of acetaminophen were 0.51 ± 0.08 hours (without coffee), 0.4 ± 0.09 hours and 0.67 ± 0.07 hours with coffee containing both doses of caffeine respectively (Figure 3). Mean absorption half-life of acetaminophen with coffee containing caffeine 65 mg was shorter by 21.5% and it was significant (P ≤ 0.001). Mean absorption half-lives of acetaminophen with coffee containing caffeine 195 mg was longer by 31.37% but not statistically significant.
The mean elimination half-lives ($T_{1/2}$) of acetaminophen were $3.65 \pm 0.11$ hours (without coffee), $4.62 \pm 0.16$ hours (with coffee containing 65 mg caffeine) and $4.58 \pm 0.12$ hours (with coffee containing 195 mg caffeine) (Figure 4). The differences in mean elimination half-lives were significant ($P < 0.001$). Mean area under concentration time-curve (AUC) values were increased by 6.92% and 43.33% respectively ($P < 0.001$).

Figure 3: Absorption half-life of acetaminophen.

Figure 4: Elimination half-life of acetaminophen.
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The mean area under the plasma concentration-time curve (AUC) of acetaminophen were $99.87 \pm 7.83 \, \mu g/mlx\, hr$ (without coffee), $106.79 \pm 6.7 \, \mu g/mlx\, hr$ (with coffee containing 65 mg caffeine) and $143.14 \pm 11.25 \, \mu g/mlx\, hr$ (with coffee containing 195 mg caffeine). Mean AUC values were increased by 6.92% and 43.33% respectively and were significant ($P < 0.001$) (Table 1).

<table>
<thead>
<tr>
<th>Title</th>
<th>Acetaminophen</th>
<th>Acetaminophen and Caffeine 65 mg</th>
<th>Acetaminophen and Caffeine 195 mg</th>
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<td>13.5 $2\mu g/ml$</td>
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<td>151 min</td>
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<td>3.46 hr</td>
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<td>above MEC</td>
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<tr>
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<td>0.4 hr</td>
<td>0.67 hr</td>
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<td>$K_{\text{el}}$</td>
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<td>106.79 $\mu g/mlx hr$</td>
<td>143.14 $\mu g/mlx hr$</td>
</tr>
</tbody>
</table>

*Table 1: The pharmacokinetics parameters of acetaminophen taken with water and with coffee containing different doses of caffeine ($K_{\text{ab}}$ means absorption rate constant and $K_{\text{el}}$ means elimination rate constant).*

Discussion

This study was done to find out the effect of coffee on the pharmacokinetic of acetaminophen. Acetaminophen has a marked inter-individual variation in first-pass effect [7].

There were 15 male subjects chosen carefully by inclusion and exclusion criteria. The study design was complete cross-over design (i.e. each subject performed as its own control) which has eliminated unnecessary variation due to subjects. The peak acetaminophen (500 mg) plasma concentration of is 10 - 20 $\mu g/ml$ [14]. This study showed that the mean peak acetaminophen serum concentrations were increased by drinking coffee with acetaminophen within therapeutic range. Therefore, it suggests that acetaminophen toxicity will not occur even when it was co-administered with coffee.

In this study, the maximum concentrations of acetaminophen were increased when acetaminophen 500 mg was taken together with coffee containing 65 mg and 195 mg caffeine showed that coffee increased the $C_{\text{max}}$ of acetaminophen significantly ($p < 0.05$). It was suggested that coffee enhances to gain target concentration of acetaminophen. The higher plasma concentration would mean better analgesic action i.e. more effective for relatively more severe pain according to pharmacokinetic principle. Consequently, higher efficacy may be obtained when acetaminophen and coffee are taken together. One study done by Nicholas., et al showed that there was a superior reduction in pain in subjects taking acetaminophen (650 mg) together with caffeine 65 mg and 130 mg than in subjects taking either acetaminophen or caffeine alone. The possible cause of pain reduction is that central nervous system stimulant effect of caffeine thought to reduce headaches by increasing a person’s sense of well-being.

Moreover, caffeine produced a significant increase in the anti-nociceptive effect of acetaminophen in rats [15].

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Caffeine at 65 mg caused a faster absorption of acetaminophen as shown by shorter $T_{\text{max}}$ while caffeine 195 mg slowed the rate of acetaminophen absorption, as shown by longer $T_{\text{max}}$. So, it is suggested that when acetaminophen is taken together with one cup of coffee containing 65 mg caffeine, it may give rise to a faster cure but not coffee containing 195 mg caffeine.

The duration of concentration above MEC of acetaminophen was significantly increased when acetaminophen was taken with coffee containing 195 mg of caffeine suggesting that higher caffeine level 195 mg may prolong action of acetaminophen. Our studied showed that AUC of acetaminophen increased by caffeine in dose dependent manner. So, the greater the amount of caffeine, the more increased in AUC which may lead to better analgesic action.

The mean plasma half-lives of acetaminophen were increased but not in dose dependent manner after taking coffee containing 65 mg and 195 mg of caffeine. The elimination rate constant reduced when acetaminophen was taken together with coffee. Hence, the smaller the $K_{el}$ showed the longer the elimination of acetaminophen. It proved that caffeine significantly slow down the elimination of acetaminophen ($P < 0.001$). It was reported that acetaminophen induced hepatic reduced glutathione (GSH) depletion was more pronounced by the co-administration of caffeine [16]. Therefore, the longer the elimination half-life of acetaminophen in this study may be depletion of hepatic reduced glutathione (GSH) induced by acetaminophen with concomitant administration of caffeine caused reduction of acetaminophen metabolism. In this study, both doses of caffeine increased AUC and $C_{\text{max}}$ of acetaminophen. This might cause greater reduction in pain.

Conclusion

The findings of this study showed that coffee can modify the pharmacokinetic effects of acetaminophen (paracetamol) by increasing peak serum concentration of acetaminophen with coffee which could reach target concentration to achieve optimal drug effect. When acetaminophen was taken together with coffee containing different doses of caffeine, there was dose-related increase in serum concentration of acetaminophen. Thus, coffee may enhance the production the optimal therapeutic effect of acetaminophen. The duration of concentration above MEC was longer when acetaminophen was taken together with coffee containing 195 mg caffeine. It was suggested that acetaminophen may have longer therapeutic effect when drinking with coffee. In this study, the findings showed that the synergistic action of acetaminophen and caffeine might be the pharmacokinetic changes of acetaminophen by coffee. Therefore, it can be suggested that taking acetaminophen together with one to three cups which contain 65 mg and 195 mg of caffeine may produce a better therapeutic outcome than acetaminophen taking alone.

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Conflict of Interest

There is no conflict of interest for our research.

Bibliography


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