Influence of acidic beverage (Coca-Cola) on pharmacokinetics of ibuprofen in healthy rabbits

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The study was aimed at determining the effect of Coca-Cola on the pharmacokinetics of ibuprofen in rabbits. In a cross-over study, ibuprofen was given orally in a dose of 56 mg/kg, prepared as 0.5% suspension in carboxymethyl cellulose (CMC) and blood samples (1 ml) were drawn at different time intervals from 0-12 hr. After a washout period of 7 days, Coca-Cola in a dose of (5 ml/kg) was administered along with ibuprofen (56 mg/kg) and blood samples were drawn from 0-12 hr. To these rabbits, 5 ml/kg Coca-Cola was administered once daily for another 7 days. On 8th day, Coca-Cola (5 ml/kg) along with ibuprofen (56 mg/kg), prepared as a suspension was administered and blood samples (1 ml each) were drawn at similar time intervals. Plasma was separated and assayed for ibuprofen by HPLC technique and various pharmacokinetic parameters were calculated. The Cmax and AUC values of ibuprofen were significantly increased after single and multiple doses of Coca-Cola, thereby indicating increased extent of absorption of ibuprofen. The results warrant the reduction of ibuprofen daily dosage, frequency when administered with Coca-Cola.

Keywords: Coca-Cola; Ibuprofen; Pharmacokinetics

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) is one of the most commonly prescribed analgesic, antipyretic and anti-inflammatory drugs for rheumatoid arthritis and osteoarthritis. It is rapidly absorbed after oral administration and peak plasma concentration is achieved within 30 min with an elimination plasma half-life of about 2 hr.

A number of factors which make it difficult to predict the dose needed to achieve a desired plasma level in a patient have been identified. These factors include variations due to absorption and distribution. Any interaction which increases the bioavailability of ibuprofen can lead to toxic effects, whereas decrease in bioavailability leads to loss of therapeutic effect.

Coca-Cola, an acidic carbonated beverage with a pH of 2.5, is widely consumed throughout the world. Fruit juices, and/or Coca-Cola are commonly consumed fluids at the time of breakfast, lunch and dinner when drugs are also taken. After Coca-Cola, increased absorption of ketocazole and itraconazole and enhanced bioavailability of carbamazepine have been reported earlier in healthy volunteers.

Ibuprofen is a strong acid with a pKa of 5.3 with a limited aqueous solubility. Therefore the present study was aimed at determining the influence of Coca-Cola on the pharmacokinetics of ibuprofen in rabbits.

The study was carried out in 8 healthy male New Zealand rabbits weighing between 1.5 and 2.5 kg. The rabbits were kept in isolation for at least 21 days prior to experimentation under standard animal housing conditions i.e. 12 hr day/night cycle and room temperature 25±2°C. Animals were fed with standard rabbit diet (Ashirwad Industries, Tripli, Punjab, India) once a day at 1500 hr and water ad libitum.

Study design

An open, cross-over design was adopted to study the influence of Coca-Cola on the pharmacokinetics of ibuprofen.

Rabbits received ibuprofen orally through intragastric tube at a dose of 56 mg/kg (which was calculated according to the surface area of the animal based on human dose) prepared as 0.5% suspension in carboxymethyl cellulose (CMC). Blood samples of 1 ml each were collected through marginal ear vein at 0.5, 1, 1.5, 2, 4, 6, 9 and 12 hr after drug administration. After a washout period of 7 days, rabbits were administered ibuprofen in a dose of 56 mg/kg prepared in 0.5% suspension of CMC along with Coca-Cola (5 ml/kg) orally after overnight fasting and...
blood samples were collected at 0.5, 1, 1.5, 2, 4, 6, 9 and 12 hr after drug administration. The rabbits continued to receive Coca-Cola (5 ml/kg) orally once daily for another 7 days. On the 8th day, rabbits were again administered ibuprofen in suspension form along with Coca-Cola (5 ml/kg) and blood samples (1 ml each) were withdrawn at similar time intervals. Plasma from each sample was separated and assayed by taking 0.2 ml of plasma to which 0.3 ml of acetonitrile was added for protein precipitation. Tubes were vortexed for 15 sec and kept at room temperature for 15 min and vortexing was repeated and tubes were centrifuged at 2500 rpm for 20 min. The supernatant of test sample was separated and 20 μl was injected directly into column using a constant volume injector at a wavelength of UV detector 220 nm at a flow rate of 1.5 ml/min. The mobile phase consisted of methanol:water (80:20 v/v) containing 1 ml of orthophosphoric acid per 1000 ml of mobile phase.

The sensitivity of the assay was 1 μg/ml, recovery 93.38% and inter-intra-assay coefficient variance was within the limit range of 10% i.e. 5.42% and 7.10% respectively.

Pharmacokinetic parameters

The following pharmacokinetic parameters were calculated assuming an open one-compartment model. The peak plasma concentration (Cmax) and the time to reach peak plasma concentration (tmax) were determined from the actual plasma data whereas elimination half-life (t1/2 el) was calculated by least square regression analysis and area under plasma concentration time curve (AUC) by the Trapezoidal rule.

Statistics

The data are expressed as mean ± SE. Statistical analysis was performed with student’s paired ‘t’ test. The data were considered to be statistically significant when P<0.05.

Figure 1 shows the mean plasma ibuprofen levels before and after single and multiple doses of Coca-Cola at different time intervals. The plasma ibuprofen levels were significantly increased from 0.5 to 2 hr after a single dose Coca-Cola and from 0.5 to 4 hr after multiple doses of Coca-Cola as compared to ibuprofen alone.

Table 1 depicts the mean±SE values of various pharmacokinetic parameters of ibuprofen before and after single and multiple doses of Coca-Cola in rabbits. The Cmax (peak plasma concentration) and AUC of ibuprofen significantly increased after single and multiple doses of Coca-Cola as compared to ibuprofen alone. The tmax (time to reach peak plasma concentration) was slightly decreased with single and multiple doses of Coca-Cola but could not reach the significant level. Similarly, no statistically significant difference was observed in the of ibuprofen before and after single and multiple doses of Coca-Cola.

![Fig. 1 - Plasma ibuprofen levels (mean ± SE) at different time intervals before and after single dose (SD) and multiple dose (MD) of Coca-Cola in rabbits. *P<0.05 as compared to ibuprofen. **P<0.05 as compared to ibuprofen + SD Coca-Cola.](image-url)
Interactions between food and drugs may inadvertently reduce or increase the drug effect and moreover food and nutritional status have been considered important factors both in absorption and metabolism of drugs. Depending upon the type of food, dietary fluids, juice etc. the nature of drug and degree of interactions, the drug absorption may be reduced, delayed, unaffected or increased. The result of the present study shows a significant increase in the extent of absorption (Cmax and AUC0-∞) of ibuprofen after single and multiple dose administration of Coca-Cola as compared to control group. Many dietary fluids, for example grape fruit juice, increase the oral bioavailability of number of drugs like nifedipine, felodipine10 and carbamazepine11.

The gastrointestinal absorption of drugs is a complex process and the rate and extent depend on several factors related to the drug itself. These factors include physicochemical properties, pharmaceutical formulation, vehicle and the site of administration. Absorption also depends on physiological conditions, such as pH and gastric emptying time and solubility. Ibuprofen is an acidic drug with a pKa of 5.3 and limited aqueous solubility in water but soluble in alcohol and chloroform12. The pH at the absorption site is important because drugs can be either weak organic acids or bases. Mostly, acidic drugs are predominantly unionized at the low pH of gastric fluids and may be absorbed from stomach as well as from intestine and moreover acidic drugs in the pKa range of 2.5 to 7.5, are greatly affected by changes in pH which may improve or impede absorption and this absorption is pH dependent. Such drugs are better absorbed from acidic conditions (2.5 to 7.5) of stomach (pH<pKa) when they largely exist in unionized form which may be the possible explanation for increase in Cmax and AUC0-∞ of ibuprofen after Coca-Cola in the present study. The bioavailability of ibuprofen was significantly increased after single and multiple dose treatment of Coca-Cola and the present study recommends further work on human volunteers and patients and if similar results are obtained as in our study, the dose frequency of daily dosage of ibuprofen may need to be reduced. This may make the drug more GIT friendly and thereby improve patient compliance.

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