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Review Article

The Effect of Single or Multiple Doses of Grapefruit Juice on the Analgesic Effect of Ibuprofen in Mice

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Abstract

Grapefruit Juice (GFJ) is a rich source of nutritional compounds but has been shown to alter the concentrations of several clinically useful drugs. Ibuprofen is a commonly used over-the counter-drug. This study aims to examine the effect of a single or multiple dose of GFJ on the analgesic effect of ibuprofen. CD1 male mice were randomly distributed into four equal groups (n=9, each). The first group served as a control, the second group was given ibuprofen (100 mg/Kg) by oral gavage, the third group was given a single dose of GFJ (10 mg/Kg) by oral gavage followed by ibuprofen and the fourth group was given a single dose of GFJ for five days and on the fifth day was given ibuprofen. The analgesic effect was tested using two methods with different mechanisms: thermal (hot plate) and chemical (acetic acid-induced abdominal constriction) pharmacologic stimuli models. Both GFJ dosing regimen significantly increased the duration of abdominal constriction test when compared with ibuprofen group and did not exert any significant effect on the hot plate effect. This suggest that GFJ may affect the peripherally modulated analgesic effect ibuprofen. The observed effect of GFJ on ibuprofen analgesic effect warrants further studies on their impact and clinical significance on humans.

Keywords: Mice; Grapefruit juice; Ibuprofen; Analgesic

Introduction

Grapefruit, a subtropical citrus tree that found mainly in China, United States of America, Mexico, Thailand and South Africa., contains several nutrients such as vitamins, minerals, polysaccharide, lipids, beta-carotene, polyphenols and flavonoids. Grapefruit Juice (GFJ) contains components such as furanocoumarins, bergamottin, naringin and naringenin that can interact with cytochrome P450 enzymes, Organic Anion Transporting Peptide (OATP) and P-glycoprotein in the small intestine [1-3]. This interaction can alter the disposition of several commonly used drugs. It has been reported, for example, that GFJ causes a significant increase in the concentration of nifedipine, atorvastatin, ranolazine, budesonide and tacrolimus [4-6]. Some of these interactions can pose a threat to patients' life such as rhabdomyolysis with the use of simvastatin and nephrotoxicity with the use of sirolimus [7-8].

Several mechanisms implicated in the GFJ-drugs interactions; however, the inhibition of the intestinal cytochrome P450 enzymes are the commonest and most recognized pathway [1]. GFJ inactivates the enteric isoenzyme CPY3A4, a major enzyme involved in the metabolism of several drugs [1, 5-6]. GFJ have been found to inactivates, but to a lesser extent and with variable clinical effects, other isoenzymes such as CYP2D6, CYP2C9 and CYP1A2 [1,5]. Other mechanisms implicated in the GJF-drug interactions are the inhibition of OATP, which mediates the transport of organic anions across the intestine, e.g. fexofenadine, the modulation of P-glycoproteins, involved in the transport of some drugs, e.g. colchicine and the inhibition of esterase activity, associated with activation of prodrugs drugs such as enalapril [4-6].

Ibuprofen, a derivative of phenyl propionic acid, is commonly used as an over the counter medication for its anti-inflammatory and analgesic effect [9]. Ibuprofen works by inhibiting prostaglandin synthesis through the inactivation of Cyclooxygenase (COX) enzymes. The cytochrome P450 enzymes involved in the metabolism of ibuprofen are CYP2C9, CYP2C8, CYP3A4 and CYP2C19. CYP2C9 is the primary isoenzyme involved and it catalyzes the formation of 3-hydroxy-ibuprofen and 2-hydroxy-ibuprofen [9-11]. CYP2C8 plays a minor role in the ibuprofen clearance and exhibits stereoselectivity, preferentially catalyzing the 2-hydroxylation of R-ibuprofen. CYP3A4 also contributes to ibuprofen clearance but mainly at high concentrations, whereas CYP2C19 appears to play a minor role [12].

The effect of GFJ on the ibuprofen action has not been well studied. Thus, the aim of this study was to describe the impact of ingestion of single and multiple doses of GFJ on some pharmacodynamic effects of ibuprofen, viz analgesia.

Material and Methods

Animals

CD1 male mice were obtained from the Small Animal House of Sultan Qaboos University. The animals (9-10 weeks old with 25-35 g of weight) were kept under standard animal housing conditions of a temperature of 22+/- 2 C and relative humidity of about 60% and with dark-light cycle 12/12 h. The mice had free access to water ad libitum and standard pellet diet. Before conducting the study, ethical approval was obtained from the Sultan Qaboos University Animal Ethics Committee (SQU/AEC/2019-20/02). Animal care and handling were performed with regulations and guidelines of the international laws.

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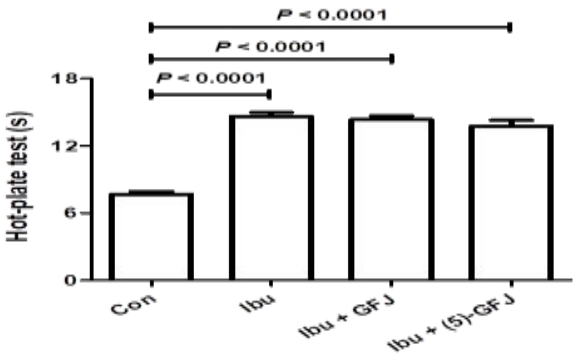

Figure 1: The effect of treatment of ibuprofen (Ibu, 100 mg/kg), alone or concomitantly with single or multiple doses of grapefruit juice (GFJ, 10 mL/kg), on time has taken (ins) for pain response on the hot plate.
Each column and vertical bar represent mean ± SEM (n=9 for each group).

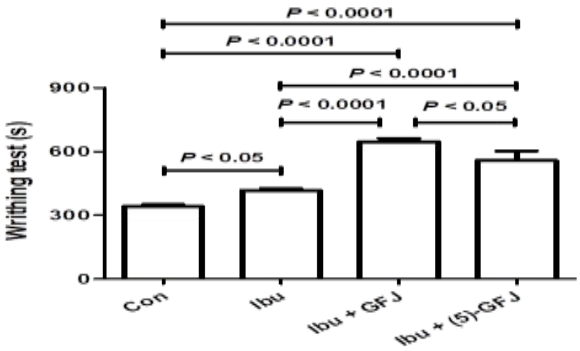

Figure 2: The effect of treatment of ibuprofen (Ibu, 100 mg/kg), alone or concomitantly with single or multiple doses of grapefruit juice (GFJ, 10 mL/kg), on time taken (ins) for the characteristic stretching behavior (writhing) during the acetic acid-induced abdominal constriction test.
Each column and vertical bar represent mean ± SEM (n=9 for each group).

Ibuprofen and GFJ

Red grapefruit was freshly purchased from a local market and squeezed on the same day of the experiment. GFJ was then filtered, centrifuged at 900g for 10 mins and stored in tubes to be ready to be administered to mice by oral gavage. Ibuprofen was brought from the Sultan Qaboos University Hospital Pharmacy. Both GFJ (10 mL/Kg) and ibuprofen (100 mg/Kg) was administered by oral gavage.

Experimental design

Following acclimatization period of one week, 36 mice were randomly divided into four equal groups (n=9). The first group served as control and received the usual diet and saline. The second group was administered ibuprofen while the third group was also given a single dose of GFJ one hour prior to administration of ibuprofen. The fourth group was administered GFJ for five days and on day five was administered ibuprofen one hour of GFJ administration.

Hot plate test

Hot plate test is used to evaluate the thermal pain sensitivity in a similar manner to what previously described [13-14]. Mice were placed on a hot metal plate that set to a temperature of 55°C on and covered by a transparent glass cylinder and the time recorded until the mice lick their jaws or jump occurs.

Abdominal constriction test

Abdominal constriction test, used to evaluate peripheral analgesic action, was performed as previously described [15]. Acetic acid (0.9% v/v) was injected intraperitoneally and five mins after administration the number of writhes (a contraction of abdominal muscles, accompanied by an elongation of the body and an extension of the hind limbs) during a 15 min period was counted.

Statistical analysis

The results are expressed as the mean ± Standard Error of Measurement (SEM). Student's two-tailed test was used to compare the groups and a p-value < 0.05 was considered statistically significant. Graph Pad Prism version 5.01 software (Graph Pad Software, Inc., San Diego, CA, USA) was used for data analysis.

Results

Hot plate test

Ibuprofen and both the single and multiple GFJ groups significantly spent a long time spent on the hot plate when compared with the control group. However, GFJ did not significantly affect either the ibuprofen effect when given in single or multiple doses (Figure 1).

Abdominal constriction test

The effect of the ibuprofen and GFJ on the duration of abdominal constriction test is depicted in (figure 2). Ibuprofen and both GFJ groups significantly increased the time duration until the mice reacted to acetic acid when compared with the control group. GFJ given in either single or multiple doses significantly had a long time when compared with ibuprofen group.

Discussion

In this study, we examined the effect of single and multiple doses of GFJ on the analgesic effect ibuprofen, a commonly used drug for analgesia in various conditions, in mice. GFJ is known to interact with a variety of therapeutic agents through several mechanisms, but the most common is *via* its effect on cytochrome P450 enzymes [1,16].

In this study, GFJ showed no significant effect on ibuprofen in the thermally induced analgesic (hot plate) test, while it significantly prolonged the duration of abdominal constriction in the chemically induced analgesic test. Both tests are commonly used as standard pharmacological models for the assessment of analgesia [17-18]. However, the hot plate test is used generally for centrally modulated analgesic effect (thermally induced), while the abdominal constriction test is used for peripherally modulated analgesic effect (chemically induced).

Acetic acid when applied causes painful reaction and inflammation in the peritoneal area and it was hypothesized that peritoneal receptors are usually the nociceptors involved in the acetic acid test making it a nonselective antinociceptive model [15]. The test causes pain by inducing inflammatory response leading to the release of several endogenous mediators such as serotonin, histamine, prostaglandins, bradykinins and substance P [15,19]. The nociceptive neurons involved in this test are sensitive to NSAIDs, to narcotics and other centrally active drugs [15,19]. The neuronal pathway for the hot plate test, on the other hand, is mediated by the dorsal horn and

higher spinothalamic tract [13, 19].

The thermal modulated pain induced hot plate method showed no statistical effect with GFJ might partially be explained by the site and degree of interaction of GFJ with ibuprofen. GFJ interaction with drugs occurs mainly at the level of the gastrointestinal tract. It is possible that more active (unmetabolized) ibuprofen became available to act at the level of the gastrointestinal tract and therefore the effect on ibuprofen with abdominal constriction test was more pronounced than the effect on hot plate test.

GFJ have been shown to affect mainly CYP3A4, the isoenzyme responsible for the metabolism of several clinically used drugs and other isoenzymes such as CYP2C9, CYP2C19 and CYP2D6 but to a lesser extent than CYP3A4 [1,5]. Ibuprofen is metabolized to different derivatives by hydroxylation reactions followed by oxidative reactions. The oxidative reactions are performed by CYP2C9, CYP2C19 and CYP2C8 [9,12]. The isoenzymes CYP2C9 and CYP2C19 are susceptible to some degree of GFJ interaction that possibly might not be enough to alter the hot plate test results.

The other mechanisms involved with GFJ interaction on drugs are OATPs, P-glycoprotein and inhibition of esterase activity [4-6]. The first two of these mechanisms cannot be ruled out as a possible way of GFJ interaction with ibuprofen and warrant further studies.

This study is not without some limitations. First, we only included tests for examining the analgesic effects of ibuprofen and these are not specific and do not test anti-inflammatory or antipyretic effects of ibuprofen. Second, a pharmacokinetic study of ibuprofen was started but was not completed due to an unforeseen technical problem. This could have provided useful data to examine the GJF effects on the concentration-time-course of ibuprofen and to relate that to its analgesic effect.

In conclusion, the ingestion of GFJ might affect the analgesic effect of the over the counter drug, ibuprofen. However, these results warrant further studies to verify the findings and to examine the implications and therapeutic significance of this interaction on animals and humans.

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