Available online on 15.03.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open access to Pharmaceutical and Medical research

© 2011-17, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited

Review Article

ARE THE SIDE EFFECTS OF PARACETAMOL BOOSTED BY CAFFEINE?

Seetha Devi A*, Kasi Rao R, Nagamani B, Ramana Reddy Ch, Venkata Krishna P

Dept. of Pharmaceutics, Hindu college of Pharmacy, Amaravati Road, Guntur, Andhra Pradesh, India

ABSTRACT

Paracetamol (acetaminophen) with caffeine is a combination medicine indicated for the temporary relief of pain and discomfort associated with a number of conditions such as headache or muscle pain. Paracetamol has a narrow safety margin and there are number of risks associated with paracetamol. It is only safe and effective when used according to directions on OTC (Over- The-Counter) and Rx labelling. However, long-term use of paracetamol increases the risk of kidney and liver failure and makes people more vulnerable to high blood pressure and strokes. Chronic or excessive administration of caffeine has been implicated in a range of dysfunctions involving the liver, renal system, gastrointestinal system, and musculature. A patient taking the combination of paracetamol with caffeine may be more likely to experience adverse effects than to get improved analgesia, compared with paracetamol alone.

Keywords: Paracetamol, Caffeine, OTC, Hepatic Toxicity

Article Info

Received 23 Jan 2017; Review Completed 13 Feb 2017; Accepted 13 Feb 2017, Available online 15 March 2017

Cite this article as:

Devi SA, Are the side effects of paracetamol boosted by caffeine?, Journal of Drug Delivery and Therapeutics. 2017; 7(2):99-101.
DOI: http://dx.doi.org/10.22270/jddt.v7i2.1388

***Address for Correspondence**

A. Seetha Devi, Professor & HOD, Dept. of Pharmaceutics, Hindu college of Pharmacy, Amaravati Road, Guntur, A.P., India-522002.
E-Mail: seethagottipati@gmail.com, (M): 9848634733

INTRODUCTION

Paracetamol (acetaminophen) with caffeine is a combination medicine indicated for the temporary relief of pain and discomfort associated with a number of conditions such as headache or muscle pain. Paracetamol is a first-line therapy of choice in adults and children with fever and pain. [1] Caffeine is used in this product to increase the pain relieving effects of paracetamol and number of risks associated with this combination [2] Acute ingestion of paracetamol more than 150–200 mg/kg for 1–6 years aged children or 7.5–10.0g for adults (70 kg weight) is considered potentially toxic [3] A highly toxic metabolite, N-acetylbenzoimino-quinone is produced in the liver due to saturation of glucuronidation, sulfation and P450-dependent GSH conjugation pathways.[4] Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. [5] In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported. Liver damage is possible in adults who have taken 10g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. Caffeine is the world's most widely consumed psychoactive drug.[6] Caffeine is found in coffee, tea, chocolate, hot chocolate, soft drinks, strawberry, black grapes, sunflower seeds, breath fresheners, alcoholic energy drinks, some medication and some herbal medicine formulations. Taken in large doses, coffee alone can cause problems.

Overdose of caffeine may produce nervousness, restlessness, insomnia, excitement, diuresis, facial flushing, muscle twitching, GI disturbance, tachycardia or cardiac arrhythmia, "rambling" flow of thought and speech, psychomotor agitation, or periods of in-

exhaustibility. The fatal oral dose of caffeine is likely around 10 g; the highest reported ingestion to have been survived is 24 g, (plasma concentration-200 mg/L). Death has been reported from intravenous injection of 3.2 g of caffeine. More than 400–500 mg caffeine administration at a time can result in caffeine intoxication due to over-stimulation of CNS. [7] Massive overdose of caffeine can result in death. [8]

COMBINATION OF PARACETAMOL WITH CAFFEINE:

The combination of paracetamol (1000 mg) with caffeine (130 mg) is a well-established analgesic combination, in which caffeine is claimed to enhance the efficacy of paracetamol.[9] However, peak plasma levels and extent of absorption are similar for paracetamol with caffeine and paracetamol alone. The benefit of medicine containing paracetamol with caffeine is uncertain. A patient taking the combination of paracetamol with caffeine may be more likely to experience adverse effects than to get improved analgesia, compared with paracetamol alone. [10]

A combination of caffeine and paracetamol could cause a risk to the liver. Large quantities of the pain-killer and caffeine appeared to increase the risk of liver damage; Caffeine tripled the amount of a toxic by-product created when paracetamol was broken down. Paracetamol (also known as N-acetyl–p-aminophenol or acetaminophen in the USA) bind to a particular type of human enzyme (P450 3A4). In the body, this enzyme binds to paracetamol to break it down. This process produces a small amount of toxic by product that is then neutralised by the liver. This same toxin is responsible for liver damage and failure in toxic alcohol-acetaminophen interactions. Caffeine binds to the same site on the cytochrome P450 enzyme as does paracetamol, therefore slowing its oxidation. The addition of caffeine disrupts the way that paracetamol binds to the enzyme. This change in binding resulted in a three-fold increase in the production of the toxic by-product of paracetamol. Caffeine increased the production of the glutathione conjugate of paracetamol by CYP3A4. Caffeine has previously been shown to activate CYP3A activity and to increase APAP hepatotoxicity. Even small increases in CYP3A are sufficient to support caffeine-enhanced APAP toxicity. CYP3A is responsible for the caffeine-mediated stimulation of APAP toxicity. That caffeine may be an additional risk factor for developing alcohol-mediated APAP hepatotoxicity. [11] It was found that caffeine increased the production of the hepatotoxic metabolite of paracetamol as providing evidence for caffeine potentiating the hepatotoxicity of paracetamol, possibly down to therapeutic doses.

Consuming caffeine at the same time or close to taking acetaminophen (Tylenol, Panadol) greatly increases the risk of liver damage in people with hepatitis. Caffeine potentiates the harmful effects of acetaminophen. Coffee oil raises serum levels of the liver enzyme alanine aminotransferase (ALT) and to lesser extent, aspartate aminotransferase (AST). Elevation of these liver enzymes may indicate injury of hepatocytes. When hepatocytes sustain damage to their membrane, ALT is released from the cytosol, whereas when hepatocytes sustain more severe damage.

Administration of large amounts of paracetamol with caffeine could lead to liver damage.[12] This study was carried out on genetically modified bacteria in very large doses. Genetically modified Escherichia coli bacteria were used in this study to produce a liver enzyme, used to break down paracetamol. This modified enzyme is also produced by human's liver. The scientists noticed that when the E. coli were exposed to large doses of paracetamol combined with caffeine they produced three times as much toxin, called N-acetyl-p-benzoquinone imine (NAPQI) produced by the enzyme as it breaks down acetaminophen.[13] People who will take certain anti-epileptic medications, including carbamazepine and phenobarbital, and those who take St. John's Wort, a popular herbal supplement, these products have been shown to boost levels of the enzyme that produces the toxic liver metabolite NAPQI, an effect that will likely be heightened when taking both acetaminophen and caffeine together.[14]

Likewise, people who drink a lot of alcohol may be at increased risk for the toxic interaction. That's because alcohol can trigger the production of yet another liver enzyme that produces the liver toxin NAPQI.

- In real life, an estimate of the dose of levels of caffeine that interact with paracetamol would be required. The researchers are reported that it would take about 10 cups of coffee on top of a normal dose of the painkiller to cause such an effect.
- A normal person would suffer adverse effects only if they drank 10 cups of strong coffee a day while taking the painkiller.

The toxic interaction could occur not only from drinking caffeinated beverages while taking the painkiller but also from using large amounts of medications that intentionally combine caffeine and acetaminophen for the treatment of migraine headaches, menstrual discomfort and other conditions.

Combination of paracetamol and caffeine is not recommended for use during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption. [15] In 2010 for pregnant women, American Congress of Obstetricians and Gynaecologists (ACOG) concluded that caffeine consumption is safe up to 200 mg per day. [16] The UK Food Standards Agency has also recommended that caffeine consumption is safe up to 200 mg per day in pregnant women.[17] Pregnant women should not consume more than 200 mg caffeine per day, as this may increase the risk of spontaneous miscarriage.

Administration of greater than 300 mg per day may also increase the risk of preterm delivery and foetal growth retardation.

Chronic or excessive use of paracetamol with caffeine is not safe. The combination of paracetamol and caffeine 500 mg/65 mg tablets is safe as OTC drug. Administration of large dose of paracetamol with caffeine might increase the risk of liver damage, renal medullary necrosis and rebound headache. [18] In case of pregnant and lactating mother this combination increases the risk of lower birth weight, spontaneous abortion, preterm delivery and foetal growth retardation. If paracetamol with caffeine has to take then do not consume more than 520 mg caffeine per day

CONCLUSION:

From the present study it is clearly demonstrated that chronic or excessive use of paracetamol with caffeine is not safe. The combination of paracetamol and caffeine 500 mg/65 mg tablets is safe as OTC drug. Administration of large dose of paracetamol with caffeine might increase the risk of liver damage, renal medullary necrosis and rebound headache. In case of pregnant and lactating mother this combination increases the risk of lower birth weight, spontaneous abortion, preterm delivery and foetal growth retardation. Patients taking combination of paracetamol with caffeine may be more prone to adverse effects than to get improved analgesia, compared with patients taking paracetamol alone. "The bottom line is that you don't have to stop taking acetaminophen or stop taking caffeine products, but you do need to monitor your intake more carefully when taking them together, especially if you drink alcohol." However further study is necessary due to some conflicting results.

REFERENCES:

1. Brune K, Renner B, Tiegs G, Acetaminophen/paracetamol: A history of errors, failures and false decisions: JAMPS, 2016; 5(3):1-18.
2. Garry GG, Kieran FS, Richard OD, Alcohol and paracetamol, Aust Prescr: JAMPS 2004; 5(3):14–15.
3. Acetaminophen toxicity, http://emedicine.medscape.com/article/820200-overview.
4. Nawrot P, Jordan S, Eastwood J, Rotstein AJ, Hugenholtz, Feeley M, Effects of caffeine on human health: Food Addi and Conta, 2003; 20(1):2-3.
5. James LP, Mayeux PR, Jack A, Acetaminophen-induced hepatotoxicity, Hinson Drug Metabolism and Disposition, The American Society for Pharmacology and Experimental Therapeutics: 2003; 31(12):1499–501.
6. Garry GG, Kieran FS, Richard OD, Alcohol and paracetamol, Aust Prescr, Journal of Advances in Medical and Pharmaceutical, Sciences: 2004, 5(3); 27:14–15.
7. Summary of product characteristics, http://www.mhra.gov.uk/home/grOups/spcpil/documents/spcpil/con1423201313476.pdf, Accessed, 20 September 2015.
8. Jack A. Hinson, Dean W. Roberts, and Laura P. James, Mechanisms of Acetaminophen-Induced Liver Necrosis Handb Exp Pharmacol: 2010; (196):369–405.
9. Mrazik DM, Reconsidering caffeine: An awake and alert new look at America's most commonly consumed drug: https://dash.harvard.edu/bitstream/handle/1/8846793/Mrazik.html?sequence=2.
10. Md. Sahab Uddin, Md. Waliullah Wali, Abdullah Al Mamun, Md. Asaduzzaman, Md. Shah Amran and Mamunur Rashid, Assessment of Risk Involved in the Combination Medicine of Paracetamol and Caffeine: JAMPS, 2016; 5(3):1-8.
11. Jaw S, Jeffery EH, Interaction of caffeine with acetaminophen: Correlation of the effect of caffeine on acetaminophen hepatotoxicity and acetaminophen bioactivation following treatment of mice with various cytochrome P450 inducing agents: Biochem Pharmacol. 1993; 46(3):493-501.
12. Ali Z, Burnett I, Eccles R, North M, Jawad M, Jawad S, et al., Efficacy of a paracetamol and caffeine combination in the treatment of the key symptoms of primary dysmenorrhoea, Curr Med Res Opin: 2007; 23:841–51.
13. Mark T. Sampson, Mixing large doses of both acetaminophen painkiller and caffeine may increase risk of liver damage for immediate release: 2007.
14. Sydney D. Nelson, Ph D, University of Washington, Acetaminophen and Caffeine Can Cause Liver Damage, Publication: Daily Health News, 2008.
15. Panadol extra (paracetamol and caffeine) for pain, http://www.nps.org.au/__data/assets/pdf_file/0009/114210/Medicine_Update_Panadol_Extra.pdf,Accessed, 2015.
16. Panadol Extra advance 500mg/65mg tablets, https://www.medicines.org.uk/emc/medicine/24353: Accessed, 20 September, 2015.
17. Paracetamol with caffeine (Panadol Extra) available over the counter from pharmacies, https://www.nps.org.au/radar/articles/paracetamol-with-caffeine-panadol-extra-available-over-the-counter-from-pharmacies: Accessed 20, September 2015.
18. Moderate caffeine consumption during pregnancy. Committee Opinion No. 462. American College of Obstetricians and Gynecologists. Obstet Gynecol 2010; 116:467–8.