



Assessment of Risk Involved in the Combination Medicine of Paracetamol and Caffeine

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Authors' contributions

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors MWW and AAM managed the literature searches and helped with author MSU. Authors MA, MSA and MR reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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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. There is a controversy going on this combination concerning their safety in patients, since 1 year later of their introduction in 1950. Paracetamol is a first-line therapy of choice in adults and children with fever and pain. Caffeine is used in this product to increase the pain relieving effects of paracetamol. 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 R_x labeling. FDA (Food and Drug Administration) drug safety communication state that prescription paracetamol products to be limited to 325 mg per tablet, capsule, or other dosage unit, making these products safer for patients. Chronic or excessive administration of

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caffeine has been implicated in a range of dysfunctions involving the liver, renal system, gastrointestinal system, and musculature. It is difficult to arrive at standard dose, since caffeine is present in various consumer goods. The extent to which caffeine improves the analgesic effect of paracetamol is in doubt. Compared with paracetamol alone, a patient taking the combination of paracetamol with caffeine may be more likely to adverse effects than to get improved analgesia. The purpose of this study is to show the risk of liver damage, renal medullary necrosis and rebound headache associated with combination medicine of paracetamol and caffeine.

Keywords: Paracetamol; caffeine; first-line therapy; controversy; doubt.

1. INTRODUCTION

Paracetamol is one of the most widely used over-the-counter antipyretic and analgesic drug for mild to moderate pain states [1,2]. This drug was discovered by an accident when instead of naphthalene acetanilide was given to patient due to a mistake at the pharmacy [3]. In 1948, Brodie and Axelrod linked the use of acetanilide with methemoglobinemia and determined that the analgesic effect of acetanilide was due to its active metabolite N-acetyl-para-aminophenol, which is also known as acetaminophen in the US and paracetamol in the UK. They advocated the use of paracetamol, since it did not have the toxic effects of acetanilide [4,5].

A combination of paracetamol, aspirin, and caffeine was first marketed in the United States in 1950 under the trade name Triagesic. In 1951 this combination drug was withdrawn from the market place due to its agranulocytosis effect. Later it was proved that this blood disease was unrelated to Triagesic [6]. In 1953 paracetamol was marketed by Sterling-Winthrop Co. as Panadol [7,8]. Paracetamol was marketed as children's Tylenol elixir by McNeil Laboratories in 1955 [9]. In 1956, 500 mg tablets of paracetamol went on sale in the United Kingdom under the trade name Panadol by Frederick Stearns & Co, a subsidiary of Sterling Drug Inc. In 1963, paracetamol was added to the British Pharmacopoeia, and has gained popularity as an analgesic agent with few side-effects and little drug-drug interactions [6].

In 2010 Panadol Extra tablets containing paracetamol 500 mg with caffeine 65 mg per tablet became an S₂ pharmacy-only medicine. Similar to paracetamol, this preparation is indicated for the temporary relief of pain and discomfort associated with a number of conditions [10].

Paracetamol is the second leading drugs commonly involved in suicide attempts and accidental poisonings [11]. Acute ingestion of

paracetamol more than 150–200 mg/kg for 1–6 years aged children or 7.5–10 g for adults (70 kg weight) is considered potentially toxic [12]. A highly toxic metabolite, N-acetylbenzoiminoquinone is produced in the liver due to saturation of glucuronidation, sulfation and P450-dependent GSH conjugation pathways [13]. Initially, the patient is asymptomatic or has mild gastrointestinal upset such as nausea, vomiting. After 24–72 hours, evidence of liver injury appears, with marked elevations in serum ALT (alanine transaminase) and AST (aspartate transaminase) levels (often to above 2000 U/L), followed at 48 to 96 hours by clinical symptoms of jaundice, confusion, hepatic failure and in some instances death. Renal failure may also occur [14]. In severe cases, fulminant liver failure occurs, leading to hepatic encephalopathy and death [15]. The severity of paracetamol poisoning is measured by determination of serum concentration of the drug. If the level of serum paracetamol concentration is greater than 150–200 mg/L approximately 4 hours after ingestion, the patient is at risk for liver injury [16]. Chronic alcoholics or patients taking drugs that enhance P450 production of toxic metabolites are at higher risk [17].

Caffeine is the world's most widely consumed psychoactive drug [18]. In case of children caffeine toxicity can cause severe emesis, tachycardia, central nervous system agitation and diuresis. Caffeine toxicity in adults is manifested by a spectrum of clinical symptoms, ranging from nervousness, irritability and insomnia to sensory disturbances, diuresis, arrhythmia, tachycardia, elevated respiration and gastrointestinal disturbances [19,20]. Even a small dose of 50 mg caffeine can cause tachycardia, anxiety and ectopic beats [10]. Chronic or excessive administration of caffeine has been implicated in a range of dysfunctions involving the liver, renal system, gastrointestinal system, and musculature [21]. Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, insomnia, restlessness, excitement, agitation,

jitteriness, tremors and convulsions [22]. More than 400–500 mg caffeine administration at a time can result in caffeine intoxication due to over-stimulation of CNS [23]. Massive overdose of caffeine can result in death [24]. Caffeine is present in different consumer products for this reason it is very difficult to attain at typical dose [25].

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 [26]. 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]. The objective of this study is to show the risk associated with combination medicine of paracetamol and caffeine.

2. RISK OF PARACETAMOL WITH CAFFEINE

Paracetamol with caffeine is a combination medicine in which caffeine is claimed to enhance the efficacy of paracetamol. However, peak plasma levels and extent of absorption are similar for paracetamol with caffeine and paracetamol alone. Patients taking the combination of paracetamol with caffeine may be more prone to adverse effects than patients taking paracetamol [10,27].

The extent to which caffeine improves the analgesic effect of paracetamol is ambiguous and may not be clinically meaningful. Published trials have assessed the effect of combining caffeine with paracetamol compared with paracetamol alone in conditions including tension-type [28] and non-migrainous headaches, [29] postoperative pain, [30,31] uterine cramping [30] and primary dysmenorrhoea [32]. Trials were generally of poor quality and had conflicting results: some showed a small benefit, most did not. For example, a trial of 320 young women found that a single dose of paracetamol with caffeine provided more pain relief for primary dysmenorrhoea 2 hours post dose than paracetamol ($P = 0.03$) but it is unclear whether this is clinically meaningful [32]. In addition, there is no evidence on the effect of repeat dosing, as only single doses were studied (2–4 hours post dose) in the trials [28-32].

2.1 Liver Damage

Administration of large amounts of paracetamol with caffeine could lead to liver damage according to the study of Nelson S, et al. [33]. 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. Team leader, Nelson said that people who take certain antiepileptic medications, such as carbamazepine, phenobarbital and those who take St. John's Wort, a popular herbal supplement may be more vulnerable to this toxic interaction than others. These drugs increase the levels of the enzyme that produces NAPQI and may produce even more when mixed with paracetamol and caffeine together [33-37].

Previous studies have already demonstrated that people who consume a large amount of alcohol are at higher risk of developing liver damage when they take paracetamol due to formation of same liver toxin, NAPQI. The risk is also increased for people who take drugs that combine paracetamol and caffeine, used to treat migraines, arthritis and other conditions. In previous studies, the same researchers showed that high doses of caffeine can increase the severity of liver damage in rats with paracetamol-induced liver damage, thus supporting the current finding [33-37].

2.2 Renal Medullary Necrosis

A study conducted by Cai Q, et al [38]. showed that chronic or excessive administration of paracetamol and caffeine causes renal medullary necrosis. This study was carried out on passage-1 rat inner medullary collecting duct (p1rIMCD) cells. Paracetamol singly and in combination with caffeine at 640 mOsmol/kg (the lowest normal inner medullary osmolality) reduce the number of proliferating (i.e., subconfluent) p1rIMCD cells. The researchers noticed that effects of paracetamol and caffeine are strongly additive. In fact addition of as little as 0.1 mM caffeine significantly enhances the toxicity of paracetamol [38].

Researchers found an unexpected novel result when p1rIMCD cells are confluent at 640 mOsmol/kg or growing very slowly at 1370 mOsmol/kg. With confluent cells at 640 mOsmol/kg and very slowly growing cells at 1370 mOsmol/kg, paracetamol significantly increases the number of p1rIMCD cells. The increase is even larger when caffeine is added with paracetamol. Associated with increased proliferation of p1rIMDC cells, paracetamol also increases the percentage of cells expressing pH2AX (gamma-H2AX phosphorylation), indicative of DNA damage. They also noticed that caffeine alone does not affect the number of confluent cells at 640 mOsmol/kg, but it adds greatly to the increase in the cell number caused by paracetamol. When p1rIMCD cells are confluent at 640 mOsmol/kg, a combination of paracetamol, salicylic acid and caffeine each significantly reduces the cell number, which is accompanied by nuclear condensation and fragmentation, indicative of apoptosis. Finally researcher conclude that paracetamol and caffeine are toxic to renal inner medullary collecting duct cells under the conditions of high osmolality normally present in the inner medulla of human, that combinations of the drugs are more toxic than paracetamol singly and that the toxicity includes induction of proliferation of these cells that are otherwise quiescent in the presence of high osmolality [38].

In previous studies, the researchers showed that chronic use of paracetamol with caffeine can causes renal medullary necrosis, using an immortalized line of mouse inner medullary collecting ducts cells (mIMCD3), thus supporting the current finding [39].

2.3 Rebound Headache

Rebound headache occurs when acute headache treatments such as analgesic medications are used too frequently [40]. Patients that take analgesics medicine 2-3 times per week on a routine basis can develop rebound headache [41]. Prolonged and frequent use of medicines containing paracetamol and caffeine increase the chance of rebound headache [10,42]. Most commonly the patient develops daily chronic headaches that can last for hours, days, or even weeks [41]. It is considered as a secondary cause of chronic daily headache with a prevalence of more than 1 to 2% [43]. Rebound headache is experienced 15 days or more days a month for at least 3 months and have developed or markedly worsened during medication overuse [44]. Paracetamol and caffeine combinations are

thought to be more likely to cause rebound headache due to the presence of two active ingredients [45].

2.4 Risk in Pregnancy

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 [46,47]. In 2010 for pregnant women American Congress of Obstetricians and Gynecologists (ACOG) concluded that caffeine consumption is safe up to 200 mg per day [48]. The UK Food Standards Agency has also recommended that caffeine consumption is safe up to 200 mg per day in pregnant women [49]. 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 [47].

2.5 Risk in Lactation

Caffeine is readily transferred to breast milk and young infants are poor metabolizers of caffeine. Newborn infants may take up to 80 hours to metabolize caffeine. Because of this long excretion time, caffeine may accumulate in significant amounts [50]. Caffeine in breast milk may potentially have a stimulating effect on breast fed infants. Infants who are breastfed by mothers consuming more than 300 mg caffeine per day may become jittery and restless, and may experience sleep difficulties. In the US, women who are breastfeeding are recommended to have no more than about 200 mg of caffeine a day [47,51].

3. MANUFACTURERS OF PARACETAMOL WITH CAFFEINE

Globally paracetamol and caffeine containing combination is widely manufactured by various pharmaceutical companies. A list of few manufacturers is given in Table 1 [52].

4. PATIENTS INFORMATION OF PARACETAMOL WITH CAFFEINE

4.1 Indications

Combination tablets of paracetamol (500 mg) and caffeine (65 mg) are used as mild to moderate analgesic and antipyretic.

Table 1. Pharmaceutical industries that manufacture combination of paracetamol and caffeine tablets [53-58]

Brand name	Generic name and strength	Manufacturer	Country
Excedrin [53]	Paracetamol 500 mg + caffeine 65 mg	Novartis Consumer Health, Inc.	USA
Sedalmex [54]	Paracetamol 500 mg + caffeine 65 mg	Midway Importing, Inc.	USA
Tylenol ultra relief [55]	Paracetamol 500 mg + caffeine 65 mg	Johnson & Johnson	Canada
Panadol extra advance [56]	Paracetamol 500 mg + caffeine 65 mg	GlaxoSmithKline	Ireland
Panadol extra [57]	Paracetamol BP 500 mg + caffeine USP 65 mg	GlaxoSmithKline Bangladesh Ltd.	Bangladesh
Napa extra [57]	Paracetamol BP 500 mg + caffeine USP 65 mg	Beximco Pharmaceuticals Ltd.	Bangladesh
Ace plus [57]	Paracetamol BP 500 mg + caffeine USP 65 mg	Square Pharmaceuticals Ltd.	Bangladesh
Action [58]	Paracetamol 500 mg + caffeine 50 mg	Flora & Pharma	India
Zoom [58]	Paracetamol 500 mg + caffeine 30 mg	Acron Pharmaceuticals	India
Anmol [58]	Paracetamol 500 mg + caffeine 50 mg	Croford Pharmaceuticals Pvt. Ltd.	India

Table 2. Dose and dosage regimen of combination of paracetamol (500 mg) and caffeine (65 mg) tablets [59]

Age	Dose and dosage regimen
Adults, the elderly and adolescents (over 15 years) who weigh between 50 kg to 60 kg.	Take 1 tablet every 4 to 6 hours as required. Do not take more than 4 tablets in any 24 hour period. Do not take more often than every 4 hours.
Adults, the elderly and adolescents (over 15 years) who weigh more than 60 kg.	Take 1 to 2 tablets every 4 to 6 hours as required. Do not take more than 6 tablets in any 24 hour period. Do not take more often than every 4 hours.

This drug is useful for the treatment of most painful and febrile conditions, such as, headache including migraine, backache, toothache, myalgia, pain of osteoarthritis, dysmenorrhea and postpartum, for relieving the fever and aches, pains of colds, flu and sore throat [59]. It is also used as adjunct therapy to treat inflammatory conditions such as rheumatoid arthritis [16].

4.2 Dose and Dosage Regimen

Each paracetamol and caffeine combination tablet contains 500 mg paracetamol and 65 mg caffeine. The maximum recommended dose of paracetamol and caffeine is two tablets (500 mg paracetamol, 65 mg caffeine in each tablet) every 4 to 6 hours, up to a maximum of 8 tablets in 24 hours (Table 2) [59].

4.3 Labelling

- Do not give paracetamol and caffeine, 500 mg and 65 mg tablets to children under 15 years or to adults or adolescents weighing less than 50 kg [60].

- Do not take more medicine than the label tells you to. If you do not get better, talk to the pharmacist or physician. If fever persists for more than 3 days or pain for more than 5 days or gets worse or other symptoms appear, stop taking this medicine and consult a physician [60].
- Do not take this product with too much caffeine in drinks like coffee, tea and some canned drinks [59].
- Do not take this product with alcoholic drinks [60].
- Do not take a double dose to make up for a forgotten dose [60].
- Talk to a physician at once if you take too much of this medicine even if you feel well [60].

5. 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. However further study is necessary due to some conflicting results.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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