sciendo Acta Marisiensis - Seria Medica 2020;66(3):127-131 DOI: 10.2478/amma-2020-0030

REVIEW

Effect of Caffeine on Pain Management

Paul Grama[1*], Miruna Pepa Oltea[2], Corina Adelina Zah[1]

1. Faculty of Medicine, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
2. Transplant and Cardiovascular Disease Institute, Targu Mures, Romania

Caffeine is a widely consumed substance, as its main intake reasons are its memory and concentration enhancing properties. Beside these well-known effects, there has been put forward a hypothesis that caffeine consumption along with antinociceptive medication can potentiate the analgesic effect of this class of drugs. Our aim was to point out the importance of this particular potentiator effect by selecting and analysing all papers on this topic written in English from the Medline database, published until the present moment. We observed that caffeine can represent a significant aid for certain patients in matters of pain management, by both reducing the pain killer doses and by increasing life quality.

Keywords: caffeine, pain management, analgesia

Received 16 April 2020 / Accepted 22 September 2020

Introduction

Caffeine is one of the most widely used psychoactive drugs of the methylxanthine class (Figure 1). Its main source are the coffee beans, but it can be also found in various concentrations in teas and cocoa beans. The use of caffeine has increased worldwide in the past decade, mainly because it boosts concentration and memory, as it stimulates the central nervous system [1]. Beside the well-known psychoactive properties, a new hypothesis has been put forward that the association of caffeine with pain relief medication can potentiate the analgesic effect of these drugs.

The aim of this review is to highlight the potential adjuvant effect of caffeine co-administered with pain relief medication.

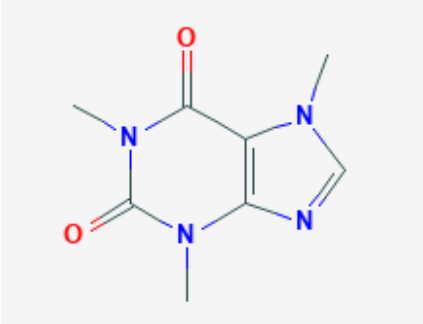

Fig. 1. Caffeine chemical structure [2]

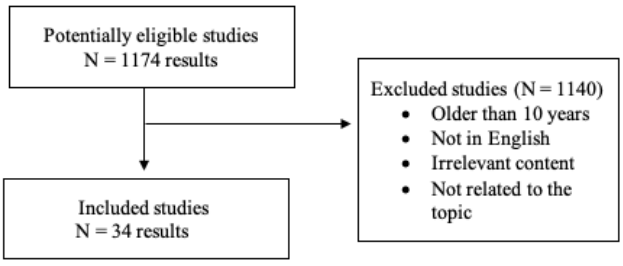

Fig. 2. Selection criteria for eligible studies

Methods

Study selection criteria

After obtaining all reports from the Medline database using the MeSH terms "caffeine" and "pain" (finding a total number of 1174), the papers were carefully analyzed in order to find data related to the topic of this review based on the following criteria: papers published in the last 10 years, written in English and with on-point content resulting a number of 34 relevant articles (Figure 2).

Caffeine pharmacodynamics

It is believed that non-selective antagonism of the A1 and A2A cell receptors of adenosine represents the most important pharmacodynamical effect of caffeine. The presence of adenosine leads to a set of physiological effects which are in opposition to those produced by caffeine. Other known mechanisms are calcium depletion from intracellular reserves and suppression of phosphodiesterase, although these effects cannot be found among the in vivo effects of caffeine administered in average doses [3]tea and soft drinks.

Caffeine pharmacokinetics

The most common route of administration is oral, reaching its plasmatic concentration peak in an interval of half an hour up to two hours, depending on the parallel food intake [4]. Absorption is completed in the small intestine and there is no evidence of a hepatic first-pass effect. There has been pointed that concentration curves are similar in both cases of oral and intravenous administration [5]. Caffeine binds to albumin in proportion of 10 to 35% [4] and the volume of distribution is 0.7 L/Kg [3]tea and soft drinks. It presents great cell-membrane permeability and it crosses the blood-brain barrier due to its lipophilic structure. Metabolization of caffeine is very complex and it comprises a high number of enzymes and intermediary

* Correspondence to: Paul Grama
E-mail: paul.grama95@gmail.com

substrates. Elimination occurs predominantly through N-demethylation to 1,7-dimethylxanthine, which is responsible for ±84% of elimination. 1,7-dimethylxanthine, or paraxanthine, is the main product of these reactions, the secondary ones being 3,7-dimethylxanthine (±11%) and 1,3-dimethylxanthine (±5%). Caffeine is metabolized in the liver by cytochrome P450, the hepatic N-demethylation being specifically catalysed by CYP1A2 (95%). All 3 dimethylxanthines can be further demethylated to monomethylxanthines.

The main metabolites present in urine are 1-methyluric acid, 5-acetylamino-6-formylamino-3-methyluracil, 1-methylxanthine, 1,7-dimethyluric acid and 1,7-dimethylxanthine. Unmetabolized caffeine is present in a small percentage (1-2%) [3]tea and soft drinks. Small traces can still be detected in saliva, bile, semen and lactation [4].

Results

Overview of caffeine and pain

A single-centre, double-blind, controlled, two-way crossover phase-1 study carried out by Weiser et al. seek to determine whether caffeine can influence the bioavailability and pharmacokinetics of paracetamol and acetylsalicylic acid by administering a fixed-dose of caffeine, acetylsalicylic acid and paracetamol. They have shown that caffeine does not influence the pharmacokinetics of the analgesic drugs but can influence their pharmacodynamic profiles leading to an enhanced analgesic effect [6].

A study conducted on rats regarding the pharmacokinetics and pharmacodynamics of ketoprofen co-administered with caffeine demonstrated that oral administration of this combination of drugs shows important advantages compared to monotherapy ketoprofen, enhancing the antinociceptive effect without affecting the pharmacokinetic processes. The study showed no pharmacokinetic interactions between caffeine and ketoprofen proving that the increased antinociceptive effect may be due to pharmacodynamic effect, but the mechanisms are not currently completely understood [7].

It has been shown that caffeine enhances early absorption of acetaminophen. The administration of caffeine and paracetamol is superior in matter of reducing both subjective perception and objective (pain-related evoked potentials) measurement of pain. The longer lasting pain relief has been explained by compartmental Pharmacokinetic-Pharmacodynamic modelling and has been linked to the difference in the equilibration half times. The authors suggest that there is a different equilibration half-time in tonic pain compared to phasic pain, suggesting different compartments involved for processing nociceptive information [8].

Several theories have been postulated on why caffeine might interfere with the pharmacokinetics of analgesic drugs.

In high doses, caffeine inhibits phosphodiesterase and stimulates nitric oxide production, both being involved in pain modulation. Other possible mechanisms may be the cholinergic activation and adenosine antagonism, which can be explained by different actions of adenosine activators and inhibitors on pre-and postsynaptic receptors in the central nervous system. Another possibility is that caffeine has the potential of activating inhibitory glycinergic transmission via presynaptic A1 receptors in the substantia gelatinosa [8].

In addition to the potentiating effects of pain medication, several reviews suggested that caffeine may play a role in pain modulation [9–11].

Migraine and Headache

Caffeine is a well-recognized competitive antagonist of adenosine and is therefore a common additive to medications for tension and migraine type headaches and is also a well-studied therapy for the treatment of post-dural puncture headaches (PDPH). Contrasting study results have linked chronic caffeine consumption to pain relief in regard to headaches. On the other hand, caffeine can also act as a trigger as high doses might be linked to the unwanted effect. Caffeine consumption has been related to chronic headaches rather than migraines [12]. A number of research papers have focused on the role of caffeine in pain modulation during migraine-type headache [13–16]. However, a prospective clinical study carried out by Lee MJ et al. on 108 patients shows that in the management of this particular type of pain with triptan-class drugs, caffeine abstinence is correlated with better treatment efficiency. Sources of caffeine included brewed or drip coffee, instant coffee, caffeinated tea, cola, and energy drink, with estimated doses of 136 mg, 96mg, 40 mg, 36mg, and 80mg. Nevertheless, being an uncontrolled study further research is needed [13].

Another prospective quasi-experimental study carried out on 70 patients compared the effects of intravenous administration of caffeine citrate and magnesium sulphate for treating acute migraine headache. In the first group, after the administration of 60 mg intravenous caffeine citrate, the median of the pain score decreased from 9 to 5 in one hour and afterwards to 3 in 2 hours. In the second group 2 g intravenous magnesium sulphate was administrated, median quantification had a more significant decrease from 8 to 2 after one hour and then to 0 after two hours. A detail that should not be ignored is that differences in sex and age between the groups were present, and that they may have influenced the data. Even if magnesium sulphate has proven to be have a stronger antinociceptive effect, caffeine still has shown good results [14].

In a double-blinded randomized study that compared the administration of ibuprofen 400mg with acetaminophen 500mg, the combination between acetylsalicylic acid 500mg and caffeine 130mg (AAC) and placebo therapy for the management of migraine headache, the results have shown that both ibuprofen and AAC administration schemes were better than placebo, but still demonstrating

that the combination between acetylsalicylic acid and caffeine had the best pain management outcome [15].

The analgesic properties of acute administration of caffeine in high single dose (300-500 mg) during already-onset episodes of headache have also been reported. Repeated low-doses do not prove to be efficient, especially in PDPH [17,18].

Basurto Ona et al. have conducted a systematic review in which they have pointed out that according to the papers they have analyzed, intravenous caffeine has shown a significant decrease in pain scores range in the case of patients with PDPH persistence when compared with placebo [19].

Dental and Trigeminal pain

A clinical study, conducted on patients that have undergone extraction of the third molar, evaluated the efficiency of different combinations of pain relief medication: ibuprofen 400mg both in monotherapy and in combination with 100mg caffeine, caffeine and placebo. Before treatment, the mean intensity among the patients was 7.7, on numerical scale from 1 to 10. The experiment proved significant superiority of the two-drug combination over the three other groups [20]. Also, combination containing acetaminophen is considered to be superior to other analgesics administered concomitant with caffeine, in dental pain [21].

In matters of trigeminal pain, it was established that caffeine has no beneficial effect, or even has the potential to decreases the therapeutic response to levetiracetam–sumatriptan [22,23].

Muscular and Bone pain

A number of studies have focused on the effect of caffeine on diminishing muscle sores induced by effort. It has been proven that it can enhance performance during physical exertion and can decrease perception of soreness in the days after [24]. They have also observed a potentiating effect when administered as adjuvant to opioid therapy in patients with fibromyalgia [25].

In a trial that targeted patients suffering from back and low-neck pain, ibuprofen 400mg with caffeine 100mg did not prove to be more efficient than ibuprofen 400mg administered alone. Moreover, none of the active treatments showed superiority over placebo [26].

Pre- and Post-Operative pain

It has been shown that single-dose ibuprofen combined with caffeine has a more potent effect than monotherapy of each drug by itself [27–29].

Another study has shown that both administration of acetaminophen combinations with caffeine or codeine results in less post-operative pain in patients receiving bone implants in posterior mandibular zone with less pain for codeine group but more postoperative swelling than those in the caffeine-acetaminophen group [30].

Another double-blind research carried out by Samieirad et al. has shown that even if analgesics containing acetaminophen 300mg plus codeine 20mg have the best outcome in matter of pain, paracetamol 300 mg plus caffeine 20 mg containing analgesics are more acceptable both in matters of pain management and swelling [31].

A study carried out by Hambrecht-wiedbusch VS et al. conducted on rats that received a 20 mg/kg dose of caffeine has proven that caffeine prevented the negative impact of previous sleep loss on mechanical hypersensitivity before surgery, by diminishing the electroencephalographic markers of sleep propensity during extended wakefulness as well as the vigilance and motor impairment caused by sleep deprivation [32].

Other effects

Research was also made on how caffeine affects the outcomes of acupuncture. Fujita et al. have conducted a study on mice which was based on the hypothesis that acupuncture exerts its analgesic effects via adenosine A1 receptor activation. Caffeine represents a potent adenosine receptor antagonist. Although caffeine administration reduced the degree of hyper-mechanosensitivity after pain-induction, it completely blocked the effect of acupuncture-induced analgesia mediated by local activation of the adenosine A1 receptor [33].

Another paper states that daily consumption of caffeine (mean doses of 162.08 ± 30.36 mg) in healthy individuals does not influence the outcome of acupuncture [34]. In the case of cancer patients with end-stage disease even opioid therapy can prove ineffective. One study has assessed the efficiency of caffeine infusion to improve potency of opioid treatment. The patients included in the study received 200 mg caffeine (study group) or saline solution (control group) intravenously once a day, for two days. The study showed no statistically significant improvement of pain scores but the administration of caffeine decreased drowsiness in all patients [35].

An oral combination of racemic flurbiprofen and caffeine has been included in a trial for evaluation of its antinociceptive effect in the case of arthritic gout-type pain in rats. After administration of racemic flurbiprofen (0.1, 1.0, 10.0, and 31.6 mg/kg) or caffeine (0.1, 1.0, 10.0, and 17.8 mg/kg) to rats, the authors evaluated the effects on a pain-induced functional impairment model. The synergic effect of the drug combination has proven efficient, caffeine improving the pharmacological efficiency and potency of flurbiprofen [36].

Discussion

Managing chronic pain may represent a particular challenge for health professionals always requiring a complex and individualized strategy. In order to improve the quality of life, antalgic therapy is one of the main methods by which functional deficiencies can be reduced. Unfortunately, as any drug it also has downsides and adverse ef-

fects even for short term use. For this particular reason, the current recommendations according to WHO pain ladder suggest the administration of the lowest efficient dose at first; this can be then followed by a gradual increase in dosage and potency [37]. However, in patients suffering from chronic pain and requiring repeated and prolonged administration, these recommendations are difficult to follow, so having a substance such as caffeine that acts in a synergic way with other antalgic medication, being able to enhance pain relief medication effects can be of great value particularly to this category of patients.

In addition to the promising results of caffeine when co-administered with antalgic medication, due to psychoactive properties it can boost brain activity and it can a induce a state of wakefulness that can help patients in reducing functional deficiencies raising performance in daily tasks.

Further research on this topic is needed in order to better understand the unique qualities of caffeine and also to change the purpose of caffeine administration from a supplement meant for energy boosting to a real drug.

Conclusion

In conclusion, physicians should keep in mind that using caffeine as an aid for pain management in certain patients, considering their status and particularities, can both lower the antalgic medication doses and improve their quality of life.

Acknowledgements

The authors would like to thank Sonia Popovici for the constructive contribution of proofreading.

Conflict of interest

None to declare.

Authors' contribution

PG - Conceptualization; Methodology; Writing – original draft
MPO - Investigation; Writing and editing
CAZ - Investigation; Writing and editing

References

1. Cappelletti S, Daria P, Sani G, Aromatario M. Caffeine : Cognitive and Physical Performance Enhancer or Psychoactive Drug ? Curr Neuropharmacol 2015;13:71–88.
2. Caffeine. Natl Cent Biotechnol Information PubChem Database, CID=2519, Https//PubchemNcbiNlmNihGov/Compound/Caffeine (Accessed Apr 11, 2020) n.d. doi:10.1111/tog.12590.
3. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. Clin Pharmacokinet 2000;39:127–53. doi:10.2165/00003088-200039020-00004.
4. Tavares C, Sakata RK. Caffeine in the Treatment of Pain. Brazilian J Anesthesiol 2012;62:387–401. doi:10.1016/S0034-7094(12)70139-3.
5. Arnaud M, Gattarini S. Caffeine, coffee, and health. Raven Press 1993:43–95. https://www.worldcat.org/title/caffeine-coffee-and-health/oclc/645863770 (accessed June 22, 2020).
6. Weiser T, Weigmann H. Effect of Caffeine on the Bioavailability and Pharmacokinetics of an Acetylsalicylic Acid- Paracetamol Combination : Results of a Phase I Study. Adv Ther 2019;36:597–607. doi:10.1007/s12325-019-0891-5.
7. Medina-Lopez R, Vara-Gama N, Soria-Arteche O, Moreno-Rocha LA, Lopez-Munoz FJ. Pharmacokinetics and Pharmacodynamics of (S) -Ketoprofen Co-Administered with Caffeine : A Preclinical Study in Arthritic Rats. Pharmaceutics 2018;10:1–12. doi:10.3390/pharmaceutics10010020.
8. Renner B, Clarke G, Grattan T, Beisel A, Mueller C, Werner U, et al. Caffeine accelerates absorption and enhances the analgesic effect of acetaminophen. J Clin Pharmacol 2007;47:715–26. doi:10.1177/0091270007299762.
9. Baratloo A, Rouhipour A, Forouzanfar MM, Safari S, Amiri M, Negida A. The Role of Caffeine in Pain Management : A Brief Literature Review. Anesth Pain Med 2016;6:1–4. doi:10.5812/aapm.33193.Review.
10. Derry C, Derry S, Moore R. Caffeine as an analgesic adjuvant for acute pain in adults (Review) 2012.
11. Yancey JR, Dattoli G. Caffeine as an Analgesic Adjuvant for Acute Pain in Adults. Am Fam Physician 2013;87:11.
12. Zaeem Z, Zhou L, Dilli E. Headaches : a Review of the Role of Dietary Factors. Curr Neurol Neurosci Rep 2016;16:1–11. doi:10.1007/s11910-016-0702-1.
13. Lee MJ, Choi HA, Choi H, Chung C. Caffeine discontinuation improves acute migraine treatment : a prospective clinic- based study. J Headache Pain 2016;17:0–5. doi:10.1186/s10194-016-0662-5.
14. Baratloo A, Mirbaha S, Kasmaei HD, Payandemehr P, Elmaraezy A, Negida A. Intravenous caffeine citrate vs . magnesium sulfate for reducing pain in patients with acute migraine headache ; a prospective quasi-experimental study. Korean J Pain 2017;30:176–82.
15. Goldstein J, Hagen M, Gold M. Results of a multicenter , double-blind , controlled , single-dose study comparing the fixed combination of acetaminophen , acetylsalicylic acid , and caffeine with ibuprofen for acute treatment of patients with severe migraine. Cephalgia 2014;34:1070–8. doi:10.1177/0333102414530527.
16. Becker WJ. Acute Migraine Treatment in Adults. Headache 2015;55:778–93. doi:10.1111/head.12550.
17. Esmaoglu A, Akpinar H, Uğur F. Oral multidose caffeine-paracetamol combination is not effective for the prophylaxis of postdural puncture headache. J Clin Anesth 2005;17:58–61. doi:10.1016/j.jclinane.2004.04.003.
18. Sawynok J. Caffeine and pain. Pain 2011;152:726–9. doi:10.1016/j.pain.2010.10.011.
19. X BO, Osorio D, X BC. Drug therapy for treating post-dural puncture headache (Review) 2015. doi:10.1002/14651858.CD007887.pub3. www.cochranelibrary.com.
20. Weiser T, Richter E, Hegewisch A, Muse DD, Lange R. Efficacy and safety of a fixed-dose combination of ibuprofen and caffeine in the management of moderate to severe dental pain after third molar extraction. Eur J Pain 2018;22:28–38. doi:10.1002/ejp.1068.
21. Abou-atme YS, Melis M, Zawawi KH. Efficacy and safety of acetaminophen and caffeine for the management of acute dental pain : A systematic review. Saudi Dent J 2019;31:417–23. doi:10.1016/j.sdentj.2019.04.008.
22. Holle D, Heber A, Naegel S, Diener H, Katsarava Z, Obermann M. Influences of smoking and caffeine consumption on trigeminal pain processing. J Headache Pain 2014;15:1–6. doi:10.1186/1129-2377-15-39.
23. Tomic MA, Pecikoza UB, Micov AM, Popovic B V, Stepanovic-Petrovic RM. The Effects of Levetiracetam, Sumatriptan, and Caffeine in a Rat Model of Trigeminal Pain: Interactions in 2-Component Combinations. Pain Analg Mech 2015;120:1385–93. doi:10.1213/ANE.0000000000000640.
24. Hurley CF, Hatfield DL, Riebe DA. The effect of caffeine ingestion on delayed onset muscle soreness. J Strength Cond Res 2013;27:3101–9. doi:10.1519/jsc.0b013e3182a99477.
25. Scott JR, Hassett AL, Brummett CM, Harris RE, Clauw DJ, Harte SE. Caffeine as an opioid analgesic adjuvant in fibromyalgia. J Pain Res 2017;10:1801–9.
26. Predel H, Ebel-bitoun C, Lange R, Weiser T. A country , multi-center parallel group trial to evaluate the ef fi cacy and safety of a fixed-dose combination of 400 mg ibuprofen and 100 mg caffeine compared with ibuprofen 400 mg and placebo in patients with acute lower back or neck p. J Pain Res 2019;12:2771–83.
27. Musselman E, Stannard D. Single-Dose Oral Ibuprofen Plus Caffeine for Acute Postoperative Pain in Adults. J PeriAnesthesia Nurs 2020;35:85–6. doi:10.1016/j.jopan.2019.10.006.
28. Bergese S, Castellon-larios K. The effectiveness of a single dose of oral ibuprofen plus caffeine in acute postoperative pain in adults. Evid Based Med 2016;21:2016.
29. Derry S, Pj W, Ra M, Derry S, Pj W, Ra M. Single dose oral ibuprofen plus ca eine for acute postoperative pain in adults (Review) 2015.

doi:10.1002/14651858.CD011509.pub2.www.cochranelibrary.com.
30. Brignardello-Petersen R. ACETAMINOPHEN PLUS CAFFEINE OR PLUS CODEINE PROBABLY RESULTS IN LESS PAIN BUT MORE SWELLING IN PATIENTS UNDERGOING PLACEMENT OF A SINGLE IMPLANT WITHOUT BONE GRAFTING IN THE POSTERIOR ZONE. J Am Dent Assoc 2017;e1:2017. doi:10.1016/j.adaj.2017.09.043.
31. Samieirad S, Afrasiabi H, Tohidi E, Qolizade M, Shaban B, Hashemipour MA, et al. Evaluation of Caffeine versus codeine for pain and swelling management after implant surgeries: A triple blind clinical trial. J Cranio-Maxillo-Facial Surg 2017:18. doi:10.1016/j.jcms.2017.06.014.
32. Hambrecht-wiedbusch VS, Gabel M, Liu LJ, John P, Colmenero A V, Vanini G. Preemptive Caffeine Administration Blocks the Increase in Postoperative Pain Caused by Previous Sleep Loss in the Rat : A Potential Role for Preoptic Adenosine A 2A Receptors in Sleep – Pain Interactions. Sleep 2017;40:1–15.
33. Fujita T, Feng C, Takano T. Presence of caffeine reversibly interferes with efficacy of acupuncture-induced analgesia. Sci Rep 2017;7:1–10. doi:10.1038/s41598-017-03542-x.
34. Cao J, Tu Y, Lang C, Vangel M, Park J, Liu J, et al. Daily Caffeine Consumption Does Not Influence Acupuncture Analgesia in Healthy Individuals : A Preliminary Study. Anesth Analg 2018;XXX:1–4. doi:10.1213/ANE.0000000000003989.
35. Suh S-Y, Choi YS, Cheul S, Kim YS, Cho K, BAe WK, et al. Caffeine as an Adjuvant Therapy to Opioids in Cancer Pain : A Randomized , Double-Blind, Placebo-Controlled Trial. J Pain Symptom Manage 2013;46:474–82. doi:10.1016/j.jpainsymman.2012.10.232.
36. Lievano-Reyes R, Perez-Mendez HI, Solis-Oba A, Jaramillo-Morales OA, Espinosa-Juarez JV, Lopez-Munoz FJ. Antinociceptive Effect of Racemic Flurbiprofen and Caffeine Co-Administration in an Arthritic Gout-Type Pain in Rats. DRUG Dev Res 2016;198:192–8. doi:10.1002/ddr.21311.
37. World Health Organization and World Health Organization, 2014. WHO's cancer pain ladder for adults.