

Caffeine in the Treatment of Pain

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Summary: Tavares C, Sakata RK – Caffeine in the Treatment of Pain.

Background and objectives: Caffeine is a widely used substance with effects on several systems, presenting characteristic of pharmacokinetic and pharmacodynamic which cause interactions with several drugs. This study's objective is to review the effects caused by caffeine.

Content: This review assesses the caffeine pharmacology, its action mechanisms, indications, contraindications, doses, interactions and adverse effects.

Conclusions: There are insufficient double-blind randomized controlled studies that assess the analgesic effect of caffeine on several painful syndromes. Patients presenting chronic pain need caution when it comes to tolerance development, abstinence and drug interaction from chronic caffeine use.

Keywords: Analgesia; Caffeine; Molecular Mechanisms of Pharmacological Action; Pain.

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INTRODUCTION

Caffeine was isolated in 1820, but the precise structure of this methylxanthine was established in the last decade of the 19th century. Its effects had not been clearly acknowledged until 1981, when the blockade of adenosine receptors was correlated with caffeine's and its analogues' stimulating properties¹. Caffeine is probably one of the psychoactive substances mostly used in the world, affecting innumerable physiological structures including: physical resistance, humor, sleep and pain². In addition to being consumed as a beverage (coffee and other drinks that contain caffeine), several analgesic drugs – mainly for headaches – contain caffeine associated with paracetamol or with non-hormonal anti-inflammatory drugs³. The objective of this study is to review caffeine pharmacology, its action mechanisms and analgesic efficacy in patients presenting chronic pain. This review has been performed using PubMed database and articles published in English since 2000 with *caffeine* and *pain* as MeSH terms.

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Chemical structure

Caffeine is an alkaloid present in over 60 plant species⁴. Its molecular structure belongs to a trimethyl xanthine group which includes its compounds intimately related: theobromine (present in cacao) and theophylline (present in tea)¹. These alkaloids are chemically similar to purines, xanthines and uric acid, all metabolically important compounds⁴.

The most common sources of caffeine are: coffee, tea, chocolate and beverages derived from cola¹. The amount of caffeine present in these beverages varies according to the plant species, coffee bean type, cacao or tea leaf, geographical location, weather, cultural practices and size of the consumed portion⁴.

The amount of caffeine present in a cup of coffee varies between 47 and 134 mg. Another important consideration is that coffee, one of the main sources of caffeine, contains hundreds of chemical compounds that may cause or potentiate effects wrongly attributed to caffeine¹.

In addition to food sources, there are innumerable drugs containing caffeine which in many occasions are sold without prescription⁴.

Caffeine is clinically used as a stimulant of the central nervous system as well as indicated to treat apnea in premature neonates⁵. In this case, it is used as caffeine citrate and administered intravenously. Another formulation is caffeine with sodium benzoate, used as a stimulant or in the treatment of headaches after subarachnoid anesthesia. It is also found in several medications for the treatment of headaches, mostly associated with anti-inflammatory and analgesic drugs³.

Pharmacology

After oral administration, maximum plasma concentration occurs between 30 minutes and 2 hours, which may be prolonged with food intake⁶. Caffeine is completely and read-

ily absorbed by the intestinal tract, showing bioavailability of 100% and high solubility both in water and non-polar organic solvents⁶. Its plasma protein binding – mainly albumin – is 10% to 35%¹ and its distribution volume is 0.6 to 0.7 L.kg⁻¹. Caffeine rapidly crosses cell membranes, as well as the blood-brain and placental barrier, reaching great concentrations throughout the body, including the brain⁷.

Twenty-five caffeine metabolites have been described up to date, being metabolized in the liver by CYP1A2 demethylation⁶. The significant differences seen in caffeine plasma concentration in each subject after administration of the same dose are mainly related to variations in metabolisms. Those variations depend on four factors: genetic polymorphisms, cytochrome P450 metabolic induction and inhibition, specific changes (gender and weight), and the presence of hepatic diseases⁴. Cytochrome P450 isoenzyme CYP1A2 subfamily metabolizes most part of caffeine through demethylation (95%), transforming it in paraxanthine (85%), theobromine (10%) and theophylline (5%). Part of the caffeine is metabolized through CYP1A2 in mono-xanthines, which are xanthine oxidase substrate⁶. N-acetyltransferase-2 metabolizes paraxanthine to AFMU. Other enzymes - such as CYP2E1 and CYP3A3 - also participate albeit to a lesser extent.

Caffeine elimination kinetics is a Michaelis-Menten type, non-linear in high doses, through enzyme saturation¹. Elimination occurs after caffeine is metabolized into other more polar compounds, such as paraxanthine and theophylline, which also promote biological activity similar to caffeine⁷. Only 1% to 2% of the caffeine dose taken is eliminated unchanged in urine¹. In adults, caffeine elimination half-life is 3 to 5 hours and its metabolites are eliminated in urine. No dose adjustment is required for renal failure⁶. In newborns, both the metabolism and the clearance rate of caffeine are reduced, only achieving the levels found in adults at 6 and 3 months, respectively; its half-life may reach up to 100 hours. In newborns, theophylline metabolism forms caffeine⁵. In smokers, its half-life is twice as high as in non-smokers⁶. In subjects who do not consume coffee, caffeine half-life is twice higher, which explains the higher incidence of intoxication in those patients⁴. Caffeine is secreted in human milk, saliva, bile and semen⁶.

Sites and mechanisms of action

Caffeine's biological effect seems to be the result of action in several molecular targets⁸⁻¹⁰:

1. Adenosine receptors
2. Phosphodiesterases
3. Calcium channels
4. GABA_A receptors
5. Others

Caffeine is a central nervous system stimulant, increasing cyclic 3.5-AMP through the inhibition of phosphodiesterase¹¹. Thus, it increases the bulbar respiratory center sensitivity to

carbon dioxide, stimulates the central respiratory impulse and increases skeletal muscle contraction, improving diaphragm contractility⁹. Apnea prevention may occur through adenosine competitive inhibition⁵.

Adenosine receptors

In 1969, adenosine stimulant effects in generating AMPc in brain slices and the blockade of this effect by caffeine were described^{6,12}. A few years before, the blockade of adenosine depressing effects in the heart caused by caffeine had been described².

In 1978, Burnstock formulated the existence of two classes of purinergic receptors, named receptors P1 (adenosine) and P2 (ATP). Methylxanthines block P1 receptors and have no effect on P2 receptors. Further studies in the early 80s showed that P1 receptors could be divided in A1-adenosine (inhibitors of adenylyl cyclase) and A2-adenosine (stimulants of adenylyl cyclase) receptors. A2 receptors could be divided in A2a (in which agonists show high affinity) and A2b (in which agonists show low affinity) receptors^{8,13}.

In 1992, A3 was discovered as a new adenosine receptor in which agonists show low affinity¹⁰. This receptor, as well as A1, is not only an adenylyl cyclase inhibitor, but also a phospholipase-C stimulant, triggering calcium signaling through the genesis of IP3¹¹.

The existence of various adenosine receptor subtypes all sensible to xanthines blockade led to the the development of selective agonists and antagonists¹.

Adenosine acts in various physiological systems and the effects are often opposed to the ones attributed to caffeine. Thus, most of caffeine pharmacological effects seems to depend on the action of adenosine antagonists on cell surface receptors^{8,10}.

Caffeine is a non-selective antagonist of adenosine receptors A1 and A2a, with an inhibition constant (K_i) of 44 and 40 μmol.L⁻¹, respectively. These concentrations correspond well to the plasma concentrations found after a diet with medium amounts of caffeine¹⁰.

Caffeine acts inhibiting adenosine receptors A1, A2a and A2b and show low affinity for A3 receptors¹². The antinociceptive effect occurs through the inhibition of A2a and A2b receptors. But the blockade of A1 receptors that occurs with low doses of caffeine causes the antinociception inhibition of medications such as amitriptyline¹³. This effect on A1 receptors may lead to a decreased analgesic effect of acupuncture and transcutaneous electrical stimulation in patients who consume caffeine either chronically or acutely¹².

Cyclic phosphodiesterases nucleotide

There are 3 natural methylxanthines: caffeine, theophylline and theobromine. They are weak competitive inhibitors of phosphodiesterase¹.

Caffeine inhibits phosphodiesterase, increasing the effect and the action duration of intracellular AMPc⁴. Therefore, the effects of catecholamines are potentiated. Methylxanthines also increase the release of catecholamines¹⁴. The inhibition constant for this effect (phosphodiesterase inhibition) is 480 $\mu\text{mol.L}^{-1}$ ¹⁰.

Calcium release

Caffeine activates the calcium channels sensible to ryanodine found in the endoplasmic and sarcoplasmic reticulum, leading to the release of intracellular calcium. Millimolar concentrations of caffeine, required to activate the channels,¹¹ also trigger other effects on calcium homeostasis such as the inhibition of channels sensible to IP3¹.

Up to date, caffeine seems to be the most potent and selective xanthine for calcium channels sensible to ryanodine¹⁵.

This effect, as well as the phosphodiesterase inhibition effect, does not seem to occur *in vivo* in regular conditions, since a much higher concentration than the caffeine therapeutic concentration (100 to 1,000 $\mu\text{mol.L}^{-1}$) is required for these effects to take place, which acquire great importance in an intoxication setting¹⁰.

GABA_A receptors

Caffeine interacts with GABA_A receptors¹. Caffeine and theophylline act as reverse antagonists or agonists in benzodiazepines' action sites¹¹; that is, they act by blocking GABA_A receptors¹².

However, the required caffeine concentrations to promote this effect are hundreds of times higher than the caffeine concentrations achieved with a regular diet¹².

Other action sites

There are other potential sites of caffeine action, but millimolar concentrations of this substance are generally required. There are several ionic channels, with neurotransmitters release and action in several enzymes⁹. The effect on enzymes and ionic channels is generally inhibitory. However, Na/K-ATPase stimulation by caffeine and theophylline occurs in millimolar concentrations^{6,8}. The activation of calcium entrance and potassium and calcium channels was also reported to have been caused by caffeine. Caffeine also seems to sensitize Mg-ATPase to the stimulating effects of calcium in the cardiac myofibrils¹.

Effects

Renal

Caffeine and theophylline diuretic and natriuretic effects are well known and both have been used to treat congestive heart failure associated edema. The diuretic effect occurs through antagonists of adenosine A1 and A2a receptors⁸.

Respiratory

Theobromine antitussive effects are well known. Caffeine is widely used to treat apnea occurring in premature newborns, with a minimum incidence of adverse effects⁵.

The xanthines' stimulating respiratory effects occur due to adenosine receptor antagonism in respiratory centers. Caffeine increases sensibility of the respiratory center to carbon gas⁶. However, peripherally, caffeine has an inhibitory effect on respiration through the blockade of adenosine A2 receptors in the carotid body⁸.

Caffeine seems to improve pulmonary function in asthmatic patients, probably due to it increasing the effect of bronchodilators¹.

Other effects

Caffeine produces antidepressant, anxiolytic, neuroprotector effects and improves cognitive function². The blockade of A2a receptors may be of value in preventing hepatic cirrhosis.

In people who do not consume coffee, caffeine half-life is twice as high, which explains a higher incidence of intoxication in this group⁴.

Indications

Caffeine citrate is exclusively used for the apnea treatment in premature neonates⁵.

Caffeine is used for the respiratory depression treatment in adults, with intramuscular or intravenous administration¹.

Xanthines and its heterocyclic analogues have been developed for Alzheimer's disease treatment¹⁶. Consuming beverages that contain caffeine seems to prevent this disease¹⁷. Studies show that in cortical neurons, intracellular calcium release is significantly higher in rats that received caffeine^{18,19}.

There is extensive literature regarding possible anticancer effects of caffeine and other xanthines^{1,2}. Caffeine's antimetastatic effect has been reported in a rat breast tumor model²⁰.

Antagonists of adenosine A2b receptors have been suggested for the treatment of type 2 diabetes mellitus, but the attempts to correlate the caffeine use to the risk of this disease were inconsistent¹¹. However, there have been reports that the intake of caffeine causes reduction in the uptake of insulin-stimulated glucose²¹.

Antagonists of adenosine A2a receptors seem to have a role in the Parkinson's disease treatment¹⁷, and the use of beverages containing caffeine seems to be associated with a lower risk to develop the disease¹⁸.

Caffeine for the treatment of pain

Caffeine has a long history as an analgesic drug adjuvant⁶. Other adenosine receptor antagonists have antinociceptive effects, and the A2b receptors seem to be the target²².

In a review, authors show preclinical studies of caffeine intrinsic antinociceptive action ⁴. The antinociceptive dose ranged between 25 and 100 mg.kg⁻¹ ¹².

The antinociception seems to occur mainly through the blockade of adenosine A2a and A2b receptors ²². Other mechanisms not related to the blockade of adenosine, such as changes in the activity and synthesis of cyclooxygenase enzymes in certain sites are also implied in the adjuvant analgesic effect of caffeine ¹².

Controlled studies

There are few controlled randomized double-blind studies that assess caffeine analgesic efficacy ⁶.

In one study, there has been improvement of the cognitive function in oncologic patients treated chronically with morphine and who received a morphine dose plus 200 mg of caffeine in bolus intravenously. A decrease in pain intensity was observed in the group of patients who received caffeine with morphine, but with no statistical difference regarding the group that received morphine with placebo ²³.

In a meta-analysis authors suggest that due to the caffeine vasoconstrictor effect caused by the adenosine receptors blockade, it may be useful for headache relief ¹². In a double-blind controlled prospective study in patients with acute onsets of migraine without aura, the use of 100 mg of caffeine associated with oral 100 mg of sodium diclofenac showed that the analgesic effect was superior to diclofenac alone or to placebo in the first hour after administration, without significant adverse effects ²⁴.

In a clinical trial in patients with tension headache, 301 patients were divided in four groups: first group patients received ibuprofen 400 mg associated to caffeine 200 mg; second group, ibuprofen 400 mg; third group, caffeine 200 mg; and fourth group, placebo. Patients in the first group showed a faster and more significant improvement of headache. The ones who received caffeine alone showed a similar improvement to those who received ibuprofen alone, and both groups showing significant difference in relation to the ones who received placebo. In addition, patients who received caffeine showed faster relief of pain than those who received ibuprofen alone. However, the ones who received caffeine reported more adverse effects – mainly nervousness, nausea and dizziness ²⁵.

Abrupt interruption in patients who make chronic use of caffeine (as in preoperative fasting, for instance) may cause abstinence syndrome starting at 12 to 24 hours, peaking at 24 to 48 hours, and lasting up to 1 week. Main symptoms are headache and fatigue, which show improvement with caffeine oral or intravenous administration ¹².

On the other hand, the regular use of caffeine may be associated to the development of migraines and daily chronic headaches mainly in children ¹².

Regarding caffeine adjuvant analgesic effect in other conditions, results are very poorly consistent, but as noted before, there are few randomized prospective controlled trials available ^{6,12}.

In postoperative pain, caffeine association seems to poorly increase the analgesic effect of paracetamol, and to provide no increase at all of ibuprofen ¹². In another study, caffeine has showed to increase and prolong the analgesic effect of paracetamol ²⁶. The authors have conducted a pharmacokinetic study and observed that caffeine accelerates paracetamol absorption. This can be explained by the blood flow increase in the gastrointestinal mucosa. In addition, both caffeine and paracetamol are cytochrome P450 substrates, and caffeine is a weak inhibitor of this enzyme.

In another study, using an ischemic pain model, authors did not obtain any analgesic effect with 10 mg.kg⁻¹ of intravenous caffeine. In this study, 17 health volunteers were assessed, who received infused caffeine or placebo with inflated tourniquet in the non-dominant arm and were required to lift up a 3 kg-weight several times until they complained of unbearable pain or until 45 minutes had passed ²⁷.

Regarding headaches after subarachnoid anesthesia, there is no double-blind randomized controlled study that proved caffeine to be effective ²⁸. In spite of that, it is widely used for such purpose at doses ranging between 300 and 500 mg ¹².

Administration modes

Caffeine may be orally administered regardless of food intake.

Caffeine citrate for injection may be orally administered ⁶. Parenterally, caffeine citrate loading dose may be infused in at least 30 minutes. Maintaining dose must be administered in at least 10 minutes. It may be administered without being diluted or diluted in glucose serum in a concentration of 10 mg.mL⁻¹ ⁴. Caffeine with sodium benzoate may be administered via intramuscular with dilution, intravenous slowly, or diluted in physiologic serum ⁶.

Caution

Caffeine should be used with caution in patients with peptic ulcer disease, gastroesophageal reflux disease, renal or hepatic function impairment or cardiovascular disease. Its use must be avoided in patients with symptomatic cardiac arrhythmias, agitation, anxiety and tremors ⁴.

Caffeine dose present in drugs ranges from 30 to 100 mg. In these cases, one should pay attention to the concomitant use of beverages and foods containing caffeine ⁷.

Caffeine associated with sodium benzoate should not be switched to the caffeine citrate formulation ⁶.

The use of sodium benzoate in neonates should be avoided as it has been associated with asphyxia syndrome. Neonates who receive caffeine citrate must be closely monitored as there is risk of necrotizing enterocolitis ⁵.

Risk factor for pregnancy is level C. Caffeine crosses the placenta, and plasma concentration in the fetus are similar to those in the mother. There are reports of teratogenic ef-

fects with the administration of high in bolus doses in animals. Moderate caffeine consumption is not associated to congenital malformations, spontaneous miscarriage, prematurity or low birth weight. Pregnant women who do not smoke or drink alcohol may consume up to 5 mg.kg.d⁻¹ according to some sources, but others limit such use to 150 mg.d⁻¹. Caffeine half-life is prolonged during the second and third semesters of pregnancy^{22,29}.

Some studies in animals showed that caffeine's possible effects when used during pregnancy are skeletal alterations, intrauterine growth retardation and low birth weight⁶. The use of a large amount of caffeine seems to be associated with miscarriage and congenital malformations in humans²².

Caffeine has shown to be present in human milk⁶.

Contraindications

It is contraindicated in cases of hypersensitivity to caffeine or to any component of the formulation²².

Pharmacological interactions

Caffeine concentration may be reduced with the induction of its metabolism. Among the inductors are the use of tobacco, carbonized meat, some vegetables, low body mass index, male subjects, and regular coffee use itself, as well as the use of rifampicin, benzodiazepines, carbamazepine, phenobarbital drugs and omeprazole. Tobacco induces caffeine metabolism and, as a result, reduces its plasma concentrations⁶. Smokers who consume coffee and quit smoking may experience caffeine intoxication symptoms as caffeine doubles its concentration in the absence of tobacco.

Caffeine concentrations may increase with the inhibition of its metabolism. This occurs in the end of pregnancy, in female patients with liver disease and obesity, in some food and alcohol intake and with the use of some medications such as antimycotic drugs (fluconazole, ketoconazole), antiarrhythmic drugs (diltiazem, verapamil), antidepressants (paroxetine, fluoxetine, fluvoxamine), antipsychotic drugs (clozapine, olanzapine), methylxanthines (theophylline), oral contraceptive, cimetidine, quinolones and allopurinol^{4,6}.

Some drugs cause an increase in caffeine effect and toxicity: quinolones (particularly ciprofloxacin and ofloxacin) and CYP1A2 inhibitors such as ketoconazole and fluvoxamine².

Caffeine may reduce sedative and anxiolytic effects of benzodiazepines and barbiturates². It increases paracetamol, acetylsalicylic acid and ergotamine absorption and bioavailability. It reduces the clearance of theophylline and competitively inhibits clozapine metabolism, which may increase their plasma concentrations and likelihood of adverse effects⁴.

Caffeine produces additive analgesic effect when simultaneously administered, particularly with non-hormonal anti-inflammatory drugs. In association with paroxetine, it may cause serotonin syndrome. In addition, it potentiates nicotine stimulant effects and intensifies alcohol, nicotine and vasoconstrictors teratogenic effects^{4,6}.

In some experimental models¹², caffeine in low doses seems to inhibit several agents' antinociceptive effects such as amitriptyline, venlafaxine, carbamazepine and paracetamol. This seems to be related to the blockade of adenosine type A1 receptors, which present antinociceptive effect¹³. This effect also seems to be important in analgesia related to acupuncture and TENS, which theoretically could be inhibited by the use of caffeine¹².

Acute adverse reactions

Due to significant variability among subjects, the same dose of caffeine may cause adverse reactions in one person and show good tolerability in another. Most frequent adverse effects are palpitation, tachycardia, gastric changes, tremor, nervousness and insomnia⁷.

High doses may cause intense anxiety, fear and anguish crisis^{6,7}. Cases of acute caffeine-induced psychosis in patients showing no psychopathology and worsening of psychotic symptoms in schizophrenic patients are described¹⁶. Both coffee and tea may form insoluble compounds when associated with psychiatric medications, reducing its efficacy when administered concomitantly⁴.

Caffeine may cause anaphylaxis and be an allergen that causes unknown urticaria among consumers of cola-derived beverages⁶.

Cardiovascular (angina, arrhythmia, chest pain, palpitation, flushing and vasodilatation), gastrointestinal (gastritis, reduction of esophageal sphincter tonus), neuromuscular skeletal (fasciculation), eye disorders (intraocular pressure increase with caffeine dose > 180 mg and miosis), renal (diuresis increase) effects and effects in the central nervous system (agitation, hallucinations, headache, delirium, restlessness, insomnia, irritability, dizziness and psychosis)⁸ are also possible.

Undesirable effects of chronic exposure

There is no clear evidence that the exaggerated use of caffeine causes a significant risk to the health of healthy subjects. Caffeine intake is not directly related to the risk of hypertension. Despite altering lipid metabolism and endothelial function, there are contradictory reports on whether or not there is an increased risk of coronary disease^{1,2}.

Caffeine reduces bone density as it may potentiate the action of glucocorticoids. It does not prevent nor limits the gain of weight in overweight patients².

There is no indication that caffeine produces nephropathy alone neither does it increase the incidence of nephropathy caused by analgesic drugs. Caffeine increases calcium excretion in the urine and is one of the multiple factors implied in female urinary incontinence. Caffeine increases sodium urinary excretion and has a diuretic effect, with intensity reduced in chronic users⁶.

Caffeine stimulates the secretion of gastric acid and colon activity. The association of the use of caffeine with the development of gastric or duodenal ulcers is not clear. However, the exaggerated use of caffeine exacerbates gastroesophageal reflux, but it is not known whether this effect is caused by caffeine or other substances contained in coffee apart from caffeine ^{2,6}.

The use of caffeine is associated to conception delay, increase of spontaneous miscarriages rates and reduction of fetal growth ⁶.

There is not enough information regarding long-term adverse effects of caffeine use in preterm neonates. In the child and adolescent population, it may cause chronic daily headaches and migraines without aura, which disappears when coffee intake is reduced or stopped ²².

In some subjects, caffeine causes pathologic sleep because it produces paradoxical sedation, an idiosyncratic phenomenon which has also been described with amphetamines. Caffeine abstinence causes hypersomnia ⁶.

Caffeine may cause anxiety, anguish crisis, abstinence, and sleep dependence and alterations ^{2,6}.

Caffeine may change the cellular cycle control functions and many mechanisms of DNA reparation, as well as increase the antagonism to exposure of mutagenic and carcinogenic potentials. Even if the results are contradictory, a correlation between pancreas cancer and the use of caffeine has been suggested. Gene K-ras mutation, the tumor marker for exocrine pancreatic cancer, increases in a dose-dependent manner with the use of coffee ²⁰.

On the other hand, several studies have related the chronic use of coffee with the risk reduction for colorretal cancer, but no prospective study confirmed this result. In addition to that, caffeine shows suppressing effects on tumor cells in experimental metastasis ^{1,20}.

Intoxication

Most frequent intoxications occur in people who consume coffee, but that happens with users who increase their regular dose or with regular consumers of caffeine high doses. Most frequent symptoms are tachycardia, restlessness, nervousness, tremor and insomnia ⁷.

Caffeine intoxication, even in a large amount, may not show due to tolerance development ⁴.

Other manifestations are: comma with pulmonary edema, arrhythmias (from sinus tachycardia to atrial or ventricular fibrillation), myocardial infarction and rhabdomyolysis ^{1,4}.

The estimated acute lethal dose in adults is 5 to 10 g, intravenously or orally. Caffeine intoxication lethal cases are described ³⁰ and there is a report of a case of a patient who survived 24 g of caffeine ³¹.

Caffeine chronic toxicity may be manifested as myopathy, hypokalemia, muscle weakness, nausea, vomiting and diarrhea and weight reduction ³⁰.

Caffeine as a drug of abuse

Caffeine classification as a drug of abuse is a polemic subject. If the definition by DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision) for dependence is taken into account, seven criteria must match to classify a patient as caffeine dependent. The majority of caffeine consumers reach at least three criteria: use caffeine in greater amounts or for a larger period than the what was initially intended, tolerance development and abstinence symptoms ^{2,7}.

Moderate consumers are the ones who consume 128 to 595 mg.dia⁻¹. Major consumers use 1,020 to 1,035 mg.dia⁻¹ ⁷.

Tolerance is defined as the need to consume an increasingly higher dose of certain substance to obtain the same effect that was obtained with the initial dose. Tolerance to caffeine is a phenomenon of quick onset, low magnitude and crossed with the ones showed with other methylxanthines, but with a distinct mechanism from other drugs such as amphetamine and methylphenidate ⁷.

The tolerance phenomenon could be justified by the non-linear accumulation of caffeine and its main metabolites in multiple-dose models ⁶.

In humans, tolerance to effects on blood pressure, heart rate, diuresis, adrenaline and noradrenaline plasma levels and renin activity, as well as on sleep alterations has been demonstrated to occur within a few days ⁷.

Behavior effects

The use of coffee and beverages that contain coffee by millions of people in the world is linked to the stimulating proprieties of caffeine. Caffeine increases alertness sensation, fights fatigue and generally provides a sensation of well-being ².

Addiction does not seem to occur, although abstinence symptoms seem to be present ⁷. In high doses and in certain subjects, uncomfortable effects may occur, such as anxiety.

The molecular targets responsible for caffeine behavior effects have been extensively investigated primarily in rodents. They are mainly caused by the blockade of adenosine receptors, but the relative role of each subtype is still under investigation. The dopaminergic system seems to be involved ¹⁶.

It is important to emphasize that caffeine's acute and chronic effects may be quite varied.

The majority of caffeine's central effects in concentrations found in beverages is due to the blockade of adenosine receptors ⁸.

Anxiolytic effects of a xanthine with an extended ring that contains an arylpiperazine component seem to be due to the agonist activity on serotonergic receptors ⁴.

Genetic aspects

The existence of a common genetic factor in the consumers of drugs acting as adjuvants, coffee use or abuse together with alcohol or tobacco, has been demonstrated. There is polymorphism for gene CYP1A2 of slow caffeine metabolizers which show greater risk for myocardial infarction ⁶.

Abstinence syndrome

The onset of the abstinence symptoms ranges from 12 to 24 hours after caffeine use interruption, with maximum intensity ranging from 24 to 48 hours and duration of 2 to 9 days. Headache is the most frequent symptom⁷. Tiredness, fatigue, reduction of short and long-term alertness state also occur. In a minor level, depressing humor, difficulty concentrating, irritability and de-motivation during work may occur as well. Most severe manifestations of the abstinence syndrome are tachycardia, shaking hands, reduction of blood pressure, motor activity and adrenaline excretion in urine³.

CONCLUSION

Caffeine is a widely consumed substance both through diet habits and medications that in many occasions are sold without a doctor's prescription. It shows many interactions with

several medications and effects in all systems, with differences regarding acute and chronic use. It may cause dependence and abstinence syndrome.

Regarding pain treatment, there are few randomized prospective controlled studies, but they seem to show an analgesic efficacy in the treatment of tension headache and migraine without aura, in addition to showing an increased and prolonged analgesic effect of paracetamol through pharmacodynamic interaction. Its use in patients with chronic pain is limited by the incidence of side effects, abstinence and the risk for dependence, although it may be useful to improve the cognitive performance in cancer patients using morphine. Regarding headaches after subarachnoid anesthesia, there are no consistent studies that prove its efficacy.

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