REVIEWS

CAFFEINE : AN ADULTERANT IN ILLICIT METHAMPHETAMINE

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ABSTRACT

Caffeine has some central nervous system (CNS) stimulating effects similar to methamphetamine. It is often found in methamphetamine as a main adulterant. Caffeine deprivation can cause withdrawal syndromes in habitual caffeine consumers, which contributes to maintenance of caffeine consumption. However, tolerance to its effects has not been reported. Caffeine could not be classified as a substance of abuse under the standard DSM criteria. However, it is listed as a doping substance because of its misusing in athletes for improving endurance. Ephedrine is the other main adulterant often found in street amphetamine and methamphetamine. It could be the left over precursor during methamphetamine synthesis. Unlike ephedrine, caffeine is not a precursor for methamphetamine synthesis. Caffeine found in methamphetamine, thus, comes from intentionally adding during the process of synthesis or packing in order to cut the cost.

Key words : caffeine, stimulating effects, adulterant

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แคฟเฟอีน : สารปนปลอมในยาบ้า

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บทคัดย่อ

แคฟเฟอีนมีฤทธิ์กระตุ้นระบบประสาทส่วนกลางบางอย่างคล้ายยาบ้า และถูกพบเป็นสารปนปลอมหลักในยาบ้าบ่อย ผู้ที่ดื่มแคฟเฟอีนเป็นประจำอาจแสดงอาการอยากแคฟเฟอีนเมื่อไม่ได้ดื่ม แต่ภาวะทนต่อฤทธิ์แคฟเฟอีน (ความต้องการปริมาณแคฟเฟอีนเพิ่มขึ้นเพื่อให้ได้รับผลเท่าเดิม) ยังไม่เคยมีรายงานถึง คาเฟอีนไม่สามารถถูกจัดเป็นสารเสพติดภายใต้เกณฑ์มาตรฐานของ DSM อย่างไรก็ดี ผลจากการใช้อย่างไม่เหมาะสมในกลุ่มนักกีฬาเพื่อเพิ่มความอดทนของร่างกาย ทำให้แคฟเฟอีนถูกกำหนดเป็นสารต้องห้ามในกลุ่มนักกีฬา Ephedrine เป็นอีกสารหนึ่งที่พบปนปลอมอยู่ในยาบ้า ซึ่งอาจมาจากการแปลง ephedrine เป็นยาบ้าในกระบวนการผลิตที่เกิดขึ้นไม่สมบูรณ์ ทำให้มี ephedrine ตกค้างอยู่ในยาบ้า แคฟเฟอีนไม่ใช่สารตั้งต้นในการผลิตยาบ้า ดังนั้นแคฟเฟอีนที่พบในยาบ้ามาจากการจงใจเติมเข้าไปในระหว่างที่ผลิตหรือระหว่างอัดเม็ดยา เพื่อลดต้นทุนการผลิต

คำสำคัญ : แคฟเฟอีน, สารกระตุ้นประสาทส่วนกลาง, สารปนปลอม

INTRODUCTION

Caffeine or 1,3,7-trimethylxanthine (figure 1) is a purine alkaloid occurring naturally in coffee and cocoa beans, kola nuts and tea leaves. It is the most widely used psychoactive substance in the world. In western society, at least 80 percent of the adult population daily consume large amounts of caffeine[1]. It is widely consumed as stimulants and snacks in coffee and cocoa based foods and most often as part of ingredients in drugs. Caffeine content in these products varies according to the species of the plant. For example, an average cup of coffee or tea contains 40-100 mg of caffeine. Cola drink (12 oz.) contains 35-55 mg of caffeine. A bar of chocolate contains up to 25 mg of caffeine per 30 g, and 32-200 mg of caffeine can be found in analgesic mixtures [2, 3].

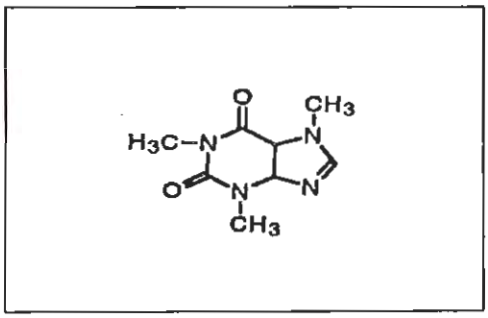

Figure 1. Structure of caffeine [2]

EFFECTS OF CAFFEINE

Consumption of tea and caffeinated beverages is associated with transient improvement in performance, rapid increase in information processing capacity and significant prevention of the steady decline in alertness and cognitive capacity[4] as well as increased rating of energetic and lively[5]. In addition, caffeine can effectively reduce early morning driver sleepiness[6] and can improve long-term memory[7]. For the psychological effect, caffeine increases arousal, but does not affect any emotion dimensions related to feeling of pleasure, or the other word, it does not induce euphoria[8]. It relaxes smooth muscle, stimulates cardiac muscle, and acts on the kidney as a diuretic. In the gastrointestinal tract, caffeine reduces mid-esophageal pressure and increases intestinal glucose absorption[9]. Caffeine increases oxygen uptake and energy expenditure rate but does not change respiratory exchange ratio. Systolic, diastolic, and mean arterial blood pressures are mildly elevated following caffeine intake[10]. The mechanism of the improvement of endurance performance by caffeine is still unknown. Caffeine ingestion is associated with an increased plasma epinephrine and cortisol levels, which might contribute to its benefit on exercise endurance[11].

TOXICITY OF CAFFEINE

There are many children suffered from headache as a result of serious lack of sleep due to the use of coffee and cola drinks[12]. In one report, caffeine intake is significantly related to self-reported parasomnias (abnormal sleeping pattern) in children[13]. Ingestion of a single oral dose of caffeine at the typical consumptive level (3 mg caffeine/kg body weight) significantly increases whole-arm physiological tremor in young adult[14]. High doses (> 3mg/kg) of caffeine in person who previously consumed little caffeine produce negative subjective effects such as nervousness, jitteriness, stomachache, and nausea[15]. Toxic manifestations in an overdose case include sweating, tachycardia, cardiac failure, pulmonary oedema, gastric dilatation, metabolic disturbances (metabolic acidosis, hyperglycaemia and creatine kinase elevation), hypertonia, and convulsion[16]. Caffeine increases gastric acid secretion, thus, patients with active peptic ulcer should restrict their intake[17]. The pressor effect (increasing blood pressure) of caffeine should be aware in patients with hypertension especially in elderly since increasing age is associated with increasing sensitivity to the pressor effects of caffeine[18,19]. Fatal caffeine poisoning is a relatively rare event but several instances have been recorded, usually after accidental or intentional ingestion of very large amounts (>3 g)[2]. Caffeine is now known to cross the placenta thus potentially could induce fetal malformation by affecting the expression of genes vital in development[3].

CAFFEINE TOLERANCE AND DEPENDENCY

Caffeine deprivation is associated with impaired vigilance performance, increased response time, decreased vigor, increased fatigue and headache, and reduced ability to work. This physical dependence occurs even under modest conditions, i.e., fewer doses per day, lower daily dose, shorter

duration of exposure. In habitual caffeine consumers, short periods of caffeine deprivation, equivalent in length to skipping regular morning coffee, produce deficits in sustained attention and noticeable unpleasant caffeine-withdrawal symptoms. Chronic caffeine user shows significant increases in typical withdrawal symptoms (e.g. sleepiness, fatigue, and mood disturbance) after stop receiving caffeine. Cessation of daily caffeine consumption significantly increases cerebral blood flow velocity leading to withdrawal symptoms of headache, drowsiness, and decreased alertness[20-23]. Chronic caffeine consumers will seek for caffeine twice as often than subjects who do not daily consume caffeine[24]. One of the significant factors motivating caffeine consumption appears to be "withdrawal relief"[25].

Not everyone who consumes caffeine-containing products shows signs of caffeine dependence and tolerance. In one survey, only 11% of the caffeine consumers reported symptoms upon stopping caffeine. Among the regular caffeine users, only 0.9% of males and 5.5% of females reported symptoms significant enough to interfere with normal activities when they abruptly stopped caffeine. When participants were unaware of the caffeine-withdrawal, both the frequency and severity of caffeine-withdrawal symptoms were very low. Therefore, clinically significant symptoms of caffeine dependence seem to be uncommon events among the general population[26]. It appears that the effects of tea and coffee are not entirely due to caffeine per se; other factors either intrinsic to the beverage (e.g. sensory attributes or the presence of other biologically active substances) or of a psychological nature (e.g. expectancy) are likely to play a significant role in tea and/or caffeine preferences [4].

After sudden caffeine cessation, withdrawal symptoms develop only in a small portion of the population but are moderate and transient. Tolerance to some subjective effects of caffeine might occur, but most of the time complete tolerance to many effects of caffeine on the central nervous system does not occur. The reinforcing stimuli functions of caffeine are limited to low or rather moderate doses while high doses are usually avoided. The classical drugs of abuse lead to quite specific increase in cerebral functional activity and dopamine release in the shell of the nucleus accumbens, the key structure for reward, motivation and addiction. However, the caffeine doses that reflect daily human consumption do not induce a release of dopamine in the shell of the nucleus accumbens but lead to a release of dopamine in the prefrontal cortex, which is consistent with caffeine reinforcing properties. Moreover, caffeine increases glucose utilization in the shell of the nucleus accumbens only at rather high doses that stimulate most brain structures, non-specifically, and likely reflect the side effects linked to high caffeine ingestion. That dose is also 5-10 folds higher than the one necessary to stimulate the caudate nucleus, which mediates motor activity, and the structures regulating sleep-wake cycle, the two functions most sensitive to caffeine[27]. When criteria for drug/substance abuse "DSM-criteria" are applied for caffeine, which include strong desire or unsuccessful attempt to stop use, spending a great deal of time with the drug, using more than intended, occurring of withdrawal symptoms, using despite knowledge of harm, occurring of tolerance and foregoing activities to use; only 7% of users meet these criteria for caffeine intoxication, and among those who have tried to stop caffeine permanently, 24% meet these research criteria for caffeine withdrawal [28].

Caffeine has weak reinforcing properties, but with little or no evidence for upward dose adjustment (tolerance), possibly because of the adverse effects of higher doses. Caffeine taken in excess, dependent on the doses, can cause flushing or chills, irritability, loss of appetite, weakness, tremor, tachycardia, vomiting, fever, convulsions, cardiac arrhythmias, coma, and death[2]. The caffeine withdrawal symptoms and its positive reinforcement effect are not pronounced as those associated with cocaine and amphetamine, nor does caffeine use appear to pose any threat to the individual or to society. There is thus no need to add diagnosis "caffeine dependence" to the psychiatric manuals[1].

COMBINATION OF CAFFEINE WITH OTHER DRUGS

Caffeine is found to be an effective analgesic adjuvant because it increases the anti-nociceptive (pain relief) effect of non-steroidal anti-inflammatory drugs (NSAIDs) while reducing the probability of side effects [29]. The co-formulation of caffeine with acetylsalicylic acid (aspirin) and acetaminophen (paracetamol) has a significant adjuvant effect and increases analgesic efficacy 1.4-1.6 folds without increasing the

nephrotoxic risk. In addition, there is no evidence to suggest that adding caffeine to analgesic mixtures could enhance the potential for promoting analgesic misuse in the general population[30].

Combination of caffeine and l-ephedrine currently is misused in athletes since it has an ergogenic effect (increasing wakefulness and endurance) on high intensity aerobic exercise performance[31]. Ephedrine, a structural analog of methamphetamine, has stimulating effects generalized to other central stimulants. The stimulus effects of l-ephedrine share some amphetaminergic commonality, but not identical[32]. Using rats trained to discriminate 1 mg/kg of d-amphetamine (ED50 = 0.4 mg/kg) from saline vehicle in a two-lever drug discrimination procedure, it is shown that l-ephedrine (ED50 = 4.5 mg/kg) could substitute for the amphetamine stimulus. In this study, caffeine (ED50 = 12.9 mg/kg) also shows to be able to substitute for d-amphetamine in a dose-related fashion. Doses of l-ephedrine and caffeine, which produced <1% drug-appropriate responding when administered alone, are able to enhance each other's stimulus effects when administered in combination such that there is a two folds leftward shift in their respective dose-response curves. It appears that low doses of l-ephedrine and caffeine mutually potentiate one another's stimulus effects in amphetamine-trained rats [33]. A case of cardiotoxicity, i.e., severe hypertension and ventricular dysrhythmias of this combination; however, has been reported, which can lead to serious morbidity and mortality if not adequately treated[34]. Ephedrine and caffeine are thus on the list of doping substances of International Olympic Committee (IOC), in order to protect the health of athletes, prevent unfair advantage (cheating) and encourage ethical behavior. Positive athletic caffeine testing is defined at the concentration in urine exceeding 12 μg/ml [35].

METHAMPHETAMINE SYNTHESIS

In the past decades, methamphetamine was synthesized in the clandestine laboratories via the reactive amination of phenyl-2-propanone (P-2-P)[36] (figure 2). After 1980's, when P-2-P became a controlled substance, synthesis of methamphetamine has changed to the conversion of ephedrine by reductive cleavage of the hydroxyl group using either thionyl chloride ($SOCl_2$) or hydriodic acid (HI) and red phosphorus[37] (figure 3). Before 1994, ephedrine was primarily used as decongestant and was found in over-the-counter cold and allergy medications in combination with antihistamines and analgesics. Now it is listed as a controlled substance and no longer found in over-the-counter drugs. The tightening of ephedrine controls is predicted to soon shift the pendulum back to the older method of synthesis, using P-2-P as a precursor, since the chemical operations required are less sophisticated[36-38]. Ephedrine is found naturally in various plants of the *Ephedra* genus, known in Chinese name "Ma Huang". It is used in a traditional Chinese medicine. The active ingredient in this plant, l-ephedrine, is also a precursor for methamphetamine synthesis. Because of the difficulty in obtaining ephedrine, Ephedra plant is currently found in clandestine laboratory for methamphetamine synthesis and seems to be a new precursor for methamphetamine synthesis[39].

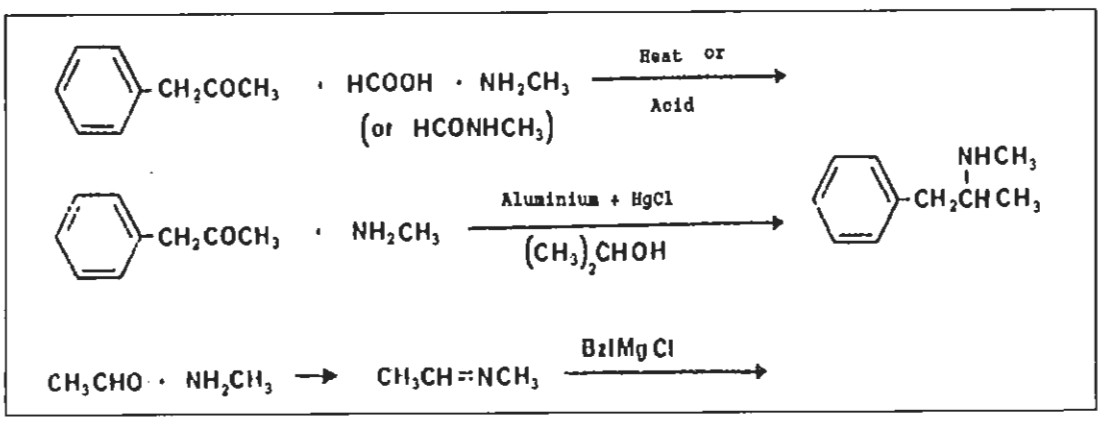

Figure 2. Synthesis of methamphetamine via reductive amination of P-2-P

The illegal synthesis of methamphetamine in clandestine laboratory is usually done by "basement-chemists" with poor quality management. There are possible various kinds of adulterants either unintentionally or intentionally added[40,41]. Caffeine is found in street methamphetamine as a cost cutting agent[42,43]. One survey found that street amphetamine and methamphetamine contained neither amphetamine nor methamphetamine. These samples contained weaker stimulants such as ephedrine and/or caffeine. Most of the samples were found to contain amphetamine or methamphetamine and other drugs, particularly ephedrine and caffeine[44]. In Thailand, Palanuvej and colleagues[45] reported that 74% of street methamphetamine contained methamphetamine and caffeine; about 13% contained methamphetamine, caffeine, and ephedrine; and 4% contained ephedrine and caffeine without methamphetamine. By structural point of view, caffeine found in the street methamphetamine is the result of adding during the process, in order to cut the cost and to avoid using controlled substance while maintaining stimulating effects although weaker than those of amphetamine. For ephedrine, it might be added into methamphetamine for the same results as that caffeine is added. In addition, it might be the left over precursor since ephedrine is a precursor for current method of methamphetamine synthesis in street market, with non-standardized, poor quality and management.

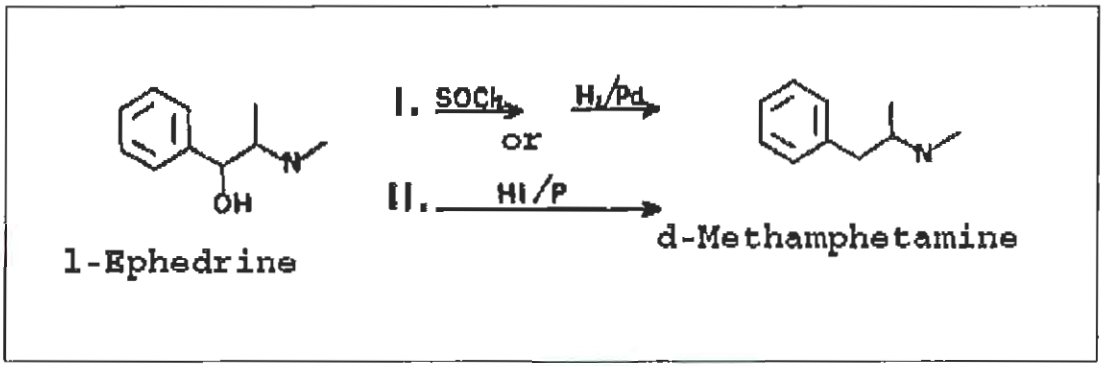

Figure 3. Synthesis of d-methamphetamine via the conversion of l-ephedrine

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