Caffeine-the Physical Dependence

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ABSTRACT

Caffeine is a xanthine alkaloid which is chemically 1,3,7-trimethyl purine therefore its give CNS stimulant activity. Caffeine are now-days used in pharmaceutical and beverages(some of the example of beverages like spike shooter, wired X344, pepsi, coca-cola, red bull etc) and also some of the pharmaceutical (example are vicks action 500 tab that contain caffeine). but there are safe dose of caffeine is 250 mg/per day. more than 250 mg/per day may cause some of the side effects like restlessness, irritability, Insomnia, nausea, but some of the positive effects of caffeine may include diuretic, memory booster, heart protective, liver protective, skeletal muscle relaxant and last found its continue consumption of caffeine may give addiction condition and further some of the withdrawal symptoms found that are anxiety, restlessness, muscle stiffness.

INTRODUCTION

Caffeine is a one of the natural substance that have a activity to central nervous system stimulant which is chemically 1,3,7-trimethyl purine-2,6-dione now a more consuming beverages and cold drink containing caffeine as a active constituents which may act as mood stabilizer and stress free. the safe dose of caffeine is 200 mg in a day may safe but addiction dose may be great than 200 mg per day, therefore addiction of caffeine chances may be great. there are many illegal psychoactive substances like tobacco, opium, but caffeine are legal to consume or sell. there are some of the beverages contain high amount of caffeine that may addicted to human being like spike shooter, cocaine energy drink etc. now a days in pharmaceutical uses caffeine are preferred, the role of caffeine is analgesic.

Further literature review caffeine consumption in the adults are found in many European countries like Denmark, Switzerland or fin...
Mechanism of action(3) -
(a) Release of Ca2+ from sarcoplasmic reticulum, especially in skeletal and cardiac muscle.
(b) Inhibition of phosphodiesterase which degrades cyclic nucleotides intracellularly. Then the concentration of cyclic nucleotides is increased. Blockade of adenosine acts as a local mediator in the CVS, CNS and smooth muscles contracts, especially bronchial dilaates cerebral blood vessels, depresses cardiac pacemaker and inhibits gastric secretion, methylxanthines produce opposite effects.

Action(a) is exerted only at concentration much higher than therapeutic plasma concentrations of caffeine (ranging from 5-20 μg/ml). Then action(b) and(c) are exerted at concentration in the therapeutic range and appear to contribute to bronchodilation, raised cAMP levels in inflammatory cells may attenuate mediator release and promote eosinophils apoptosis adding to the therapeutic effect. theophylline in asthma, adenosine A1 receptor antagonism is con- 

Pharmacological actions(3)-
1) Kidney- methylxanthines are mild diuretics; it act by inhibiting tubular reabsorption of Na+ and water as well as increased kidney blood flow.
2) Smooth muscles- all smooth muscles are relaxed, most prominent effect is exerted on bronchi, especially in asthmatics, then slow and sustained dose-related bronchodilation is produced, but the effect is much less marked compared to inhaled β2 agonists, but vital capacity is increased, pelvic spasm is relieved and effect on intestines and urinary tract is negligible.
3) Stomach- methylxanthines enhance secretion of acid and pepsin in stomach, even on parenteral injection and also gastric irritation.
4) Skeletal muscles- caffeine enhances contracile power of skeletal muscles, at high concentration, it increases releases of Ca2+ from sarcoplasmic reticulum by direct action, but at low doses twitch response to nerve stimulation is augmented, while at toxic doses contracture is produced.

In addition, caffeine facilitates neuromuscular transmission by increasing ACh release and its central action relieves fatigue and its central action relieves fatigue and increases muscle strength, especially in persons who are not habituated to caffeine. Theophylline enhances contracile power of smooth muscles, at high concentration, it increases releases of Ca2+ from sarcoplasmic reticulum by direct action, but at low doses twitch response to nerve stimulation is augmented, while at toxic doses contracture is produced.

Pharmaceutical actions(3)-
5) CNS- methylxanthines directly CNS stimulant, primarily affect the higher centres, caffeine 150-250 mg produces a sense of well-being, alertness, less drowsiness, and even when dosing has reached a sustained intellectual effort. It tends to improve performance and increase motor activity than theophylline in producing these effects, higher doses cause nervousness, restlessness, panic, insomnia and excitements, still higher doses produces tremors, delirium and convulsions. Theophylline has greater propensity to produce these adverse effects at higher doses and is definitely more toxic than caffeine. They also stimulate medullary vagal, respiratory and vasomotor centres, vomiting at high doses is due to gastric irritation and C7Z stimulation.

6) CVS- methylxanthines directly stimulate the heart and increase force of myocardial contractions. They tend to increase heart rate by direct action, but decrease it by causing vagal stimulation. Net effect is variable, tachycardia is more common with theophylline, but caffeine generally decreases heart rate. Cardiac output and cardiac work are increased at high doses cardiac arrhythmias may be produced.

While consumption of >9 cups of coffee per day has been found to be associated with increased incidence of methylxanthines, moderate ingestion of caffeine (upto 500 mg/day) does not increase frequency or severity of cardiac arrhythmias, even in the patients with ischaemic heart diseases or preexisting ventricular extra-styloids.

Methylxanthines, especially theophylline dilate systemic blood vessels including coronary by direct actions, peripheral vessels is reduced, however, cranial vessels are constricted especially by caffeine; this is one of the basis of its use in migraine.

7) Theophylline decreases release of histamines and other mediator from mast cells and activated inflammatory cells. This may contribute to its therapeutic effects in bronchial asthma.

Pharmacokinetics of caffeine- 
1) Absorption - Absorption or bioavailability of caffeine are comparable with all species like human, dogs, rats and mice, but in animals and humans caffeine is rapidly and completely absorbed in the GIT. then in human beings caffeine is 99% absorbed within 45 minutes. Therefore the plasma concentration of caffeine may decreases rapidly as compare to the paraxanthine. The pharmacokinetics of caffeine is after taking into respiratory system and IV administration are quite similar then it is absorption more in the acidic environment.

2) Distribution - Caffeine are lipid-soluble compound and therefore it enters blood brain-barrier and placental barrier, then its enter tissue-water compartments and is evenly distributed in all blood plasma, especially in the factor like saliva, semen, breast milk and bile. It mechanisms by passive diffusion in a cell layer.

3) Metabolism - Caffeine is metabolized by the two reaction, one is oxidation at C8 phosphodiesterase which degrades cyclic nucleotides intracellularly. The concentration of cyclic nucleotides is increased. Blockade of adenosine acts as a local mediator in the CVS, CNS and smooth muscles contracts, especially bronchial dilaates cerebral blood vessels, depresses cardiac pacemaker and inhibits gastric secretion, methylxanthines produce opposite effects.

Pharmacodynamics of caffeine(4)-
It acts as an adenosine A2A receptor (ADORAZA) which have ability to perform a stimulating and reinforcing properties of caffeine.

Genetics (42) - Caffeine dependence study on the heredity of human as comparing to the monozygotic and dizygotic twin and it depends upon polymorphisms in the A2A receptor gene.

Positive of caffeine(1) -
* It improves respiratory flow in body and less chances of respiratory disorders.
Caffeine is a xanthine alkaloid that serves as a stimulant. It is naturally found in the leaves of the coffee plant and other Sources like tea and chocolate. Caffeine acts as an antagonist of adenosine receptors and also increases or decreases activity of cyclic AMP at the receptor affinity.

**Additional Mechanism of Caffeine**

Caffeine acts as an antagonist of adenosine receptors and also release purine hormone that present on A1 and A2 receptors that may increase or decrease activity of cyclic AMP at the receptor affinity are different for A1 and A2 because one is high and another is low. Location of adenosine receptor is brain, cardiovascular, respiratory, renal and gastrointestinal but also in adipose tissue. Adenosine receptor non-selectively block by caffeine, concentration of caffeine depends upon intake of caffeine containing products. Another concept about adenosine that presynaptically it inhibits ach, GABA, dopamine, adrenaline and also serotonin or increasing catecholamine’s concentration and reverse the inhibitory effect to the adenosine.(31)

**Caffeine-physical dependence**

Caffeine that may produce high degree of withdrawal or tolerance that many coffee consumer prefer caffeinated coffee or not decaffeinated coffee.(31)

**Caffeine addiction or not**

Many doctors tell that high coffee consumption is harmful to health but they do not respond to it, that condition they found will addicted, there are three parameter for addiction-psycho activity, drug-reinforced behavior or compulsive use, caffeine may psychoactive therefore; coffee consuming is high, that telling reinforced to consumption and depend upon dose or producing dysphoria but addiction of caffeine is not cleared but physical dependence.(31)

**Conclusion**

Caffeine are xanthine alkaloids therefore consumption of more than 250 mg/per day may be toxic and consumer became addict with caffeine and further some of the extra dose of caffeine give following symptoms like insomnia, heartburn or some of the withdrawal symptoms like anxiety, restlessness or muscle stiffness, pregnant woman and small child must be administration of caffeine with special care. Caffeine administration will be clearly monitored and limited.

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