Al-Salam Journal for Medical Science
Journal Homepage: http://journal.alsalam.edu.iq/index.php/ajbms
e-ISSN: 2959-5398, p-ISSN: 2958-0870

Determination of coffee extract level in saliva Orthodontic patient

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DOI: https://doi.org/10.55145/ajbms.2023.1.2.001
Received September 2022; Accepted January 2023; Available online March 2023

ABSTRACT: Aim: this study was aimed to find out the pharmacokinetic of caffeine (the active compound in coffee) to determine the elimination half-life, area under the curve and other pharmacokinetic parameters for caffeine after excretion in saliva. Materials and Methods: data were collected from twenty orthodontic patients wearing fixed appliance treated in AL Noor center for at least 2 months. Each patient took one cup of coffee (100 ml), then salivary sample was collected at 0, 10, 20, 30, 45 min, 1, 2 and 3 hr. then the concentration of caffeine was detected in every sample. Results: The pharmacokinetic results for caffeine were, elimination rate constant was (0.69hr-1) by NCOMP and (0.69013hr-1) by equation, elimination half-life (1.00hr) and (1.0041hr), volume of distribution (18.17L\kg) and (17.5265L\kg), rate of clearness (10.32 L-1\hr\kg) and (12.0957 L-1\hr\kg), maximum concentration was (15.52 mg) and (15.521 mg). Conclusion: Caffeine pharmacokinetic study shows that caffeine excretes in saliva and has short half-life equal to one hr.

Keywords: Caffein, Saliva, Pharmacokinetic, Orthodontic patients

1. INTRODUCTION

Coffee is very widely consumed around the world due to its flavor and taste; it is highly used beverage on daily bases for increasing attention decreasing fatigue and giving energy especially among students and employers. The two most important varieties of commercial coffee are Coffea Arabica and Coffea Canephora, usually known as Arabica and Robusta, respectively. Coffee is known to contain over 1000 chemical compounds that contribute to both the taste and aroma of coffee [1]. Although caffeine is the most well know molecule and although it is a bitter compound, it only contributes about 15% of coffee's bitter compounds, Caffeine (Figure 1) is methylxanthine class. Caffeine is similar in chemical structure to Theophylline and Theobromine. Caffeine stimulates the CNS, heightening alertness, and sometimes causing restlessness and agitation. It relaxes smooth muscle, stimulates the contraction of cardiac muscle, and enhances athletic performance. Caffeine promotes gastric acid secretion and increases gastrointestinal motility. It is often combined in products with analgesics and ergot alkaloids, relieving the symptoms of migraine and other types of headaches [2]. Caffeine acts as a mild diuretic for certain respiratory conditions of premature newborn, pain relief, and to combat drowsiness. Caffeine is also used in a variety of cosmetic products and can be administered topically, orally, by inhalation, or by injection [3].

Figure (1): Caffeine Structure [4].

The caffeine citrate injection, is used in premature newborn. In addition, it is indicated in combination with sodium benzoate to treat respiratory depression resulting from an overdose for CNS depressant drugs. Caffeine has a broad range of over the counter uses, and is found in energy supplements, caffeine exerts several actions on cells, but the clinical relevance is poorly understood. One probable mechanism (as shown in figure 2) is the inhibition of nucleotide phosphodiesterase enzymes, adenosine receptors, regulation of calcium handling in cells, and participation in adenosine receptor antagonism. Phosphodiesterase enzymes regulate cell function via actions on second messengers cAMP and cGMP. This causes lipolysis through activation of hormone-sensitive lipases, releasing fatty acids and glycerol [5].

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Figure (2): Caffeine Mechanism of Action [6]

Pharmacokinetics, sometimes is described as what the body does to a drug, refers to the movement of drug into, through and out of the body and the time course of its absorption, bioavailability, distribution, metabolism, and excretion [7]. Drugs inside the living body undergo a process of absorption, distribution, metabolism and excretion. Elimination of drugs occur through major route which is renal system, liver and intestine, also some drugs excreted through minor route also, as lung, bile, milk and saliva [8]. Salivary excretion is not a method of drug excretion as the drug will usually be swallowed and reabsorbed. This can be called drug recycling. However, salivary elimination can be defined as the drugs that secreted by saliva gain access to oral environment from the systemic circulation and can affect the microorganisms and tissue surfaces of the mouth [9]. Drug may enter the oral fluids from several sources by passive diffusion method crossing the cells of salivary gland, or by a passive diffusion route crossing the oral epithelium. Additionally it could flow to the fluid from gingival cervices. Salivary drug elimination appears to be demented on pH portion and protein binding. This mechanism appears attractive in terms of drug monitoring example of drugs secreted in saliva, Aspirin, Phenytoin, Ampicillin, Diazepam, Penicillin, Tetracycline, Phenobarbital and Vitamins [10]. As a result, the pH of saliva varies from 6.2 to 7.6 so unionized lipid soluble drugs are excreted passively. The bitter taste in the mouth of a patient is an indication of drug excreted [11]. This research was aimed to study the pharmacokinetic of the active compounds for systemically active products caffeine and to determine the elimination half-life, area under the curve.

NCOMP (Noncompartmental Analysis of Pharmacokinetic Data) version 2.7 presents interactive and graphical surroundings for noncompartmental analysis of pharmacokinetic data via facilitating estimation of the zero and first moments of concentration - time statistics which was invented by Paul B. Laub, Fox Chase Cancer Center, Philadelphia, USA in 1995 [12]. It provides us with the following pharmacokinetic parameters: Elimination rate constant (ke): fraction of drug depleted in the organism per unit of time (Ke = CL / Vd). Half–Life t1/2: it is the time required for drug to be reduced by halving its amounts in the organism (Half-life = 0.693/Ke). Volume of Distribution (Vd): it is a proportionality variable comparing the volume of the medicine in the organism to the concentration of the medicine found in the biological fluid (Vd = A/Cp) A: drug amount in the organism at a specific time.

Cp: plasma concentration at that time. Total Clearance (Cl): drug elimination from the organism (Cl = Ke * Vd). Area under curve (AUC): The region below the plasma drug concentration-time curve (AUC) represents real pharmaceutical body exposure after administration of the medication dose and is described in mg*hr / L (AUC = C0 * Ke). Area under moment curve (AUMC): it is the entire area below the first moment curve. If concentration is plotted over time the first moment curve is prepared (AUMC = Vd * (AUC)2 / dose). Mean Residence Time (MRT): it is hypothetical estimated time for drug to stay in the organism (MRT = AUMC/AUC – T ½). Time Maximum (Tmax): peak time for drug to reach its peak plasma concentration. Concentration Maximum (Cmax): highest concentration of drug in plasma at specific time.

2. MATERIALS AND METHODS

Study sample:

The study protocol was reviewed and approved by the scientific committee of Nineveh Health Directorate, Mosul, Iraq NO.26139 and by Committee of Higher Studies-Collage of Dentistry- University of Mosul no: D.R.1768 date 1\7\2019. Study was consisting of 20 orthodontic patients, with a mean age (16.33 ± 3.51) years who had at least have 2 months wearing the orthodontic appliance.

In this study, health patient without concomitate other mouth or systemic disease, non-smoker, non-alcoholic, without known allergic history to any of our tested materials, without history of any complication after orthodontic application and patients wasn't currently on prescribed drugs were included.

Sampling and intervention

twenty orthodontic patients were informed not to brush their teeth or use any mouthwash or other have any other oral hygiene procedure for up to 12 hrs. and were informed not to eat or drink anything for two hrs. before starting of the testing procedure. Each patient took one cup of coffee (100 ml) was given to orthodontic patients. The coffee used in this study is Hamwi café. After coffe consumption salivary sample was collected from each orthodontic patient at 0, 10, 20, 30, 45 min, 1, 2 and 3 hr. The unstimulated saliva sample was collected by using Salivette which contains a cotton roll that rolled or sucked all over patient mouth for 3 min, this an easier, sanitation and clean procedure that allow saliva to be absorbed into the cotton roll. the saliva samples were separated by centrifuge, marked and stored in a freezer at (-20) C° which was controlled by specific thermometer, until measured concentration of active compounds in saliva by spectrophotometer (6).

Preparation of Caffeine Standard

10 mg of pure caffeine (from Molekula, Durham, United Kingdom, the purity of standard powders had been checked by using Bruker Tensor 27 IR spectrophotometer in the region (400-2000cm-1)) weight by three digits electronic balance, then dissolved it with small volume of deionized water in a Beker. Then, poured the mixture in a

volumetric flask and complete the volume to 100 ml by addition of deionized water to prepare 100 ppm of caffeine standard solution. After that prepared different concentrations 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80 and 90 ppm of caffeine standard solutions by dilution from 100 ppm of caffeine standard solution.

Analyzing of Standard Solution and Saliva Sample by Spectrophotometer

Caffeine concentration in standard solution (that prepared previously) and saliva samples (that had been collected previously) had been read by UV/VIS spectrophotometer with double beam optical system (by Labomed, USA) at chemical lab in College of Dentistry at Mosul University. The transmittance of caffeine samples was measured at 272.5 nm [13].

Pharmacokinetic Study for Systemic Products by Equation and Compare Result with NCOMP (Noncompartmental Analysis of Pharmacokinetic Data).

3. RESULTS

The pharmacokinetic results for caffeine (dose=200mg\100ml) [14] after taking one cup of coffee were, elimination rate constant was (0.69hr-1) by NCOMP and (0.69013hr-1) by equation, elimination half-life (1.00hr) and (1.0041hr), volume of distribution (18.17L\kg) and (17.5265L\kg), rate of clearness (10.32 L-1\hr\kg) and (12.0957 L-1\hr\kg), maximum concentration was (15.52 mg) and (15.521 mg), time of maximum concentration was (0.5hr) and (0.5hr), area under curve was (16.49 mg*hr/ml) and (18.408 mg*hr/ml), area under moment curve was (34.12 mg*hr2/ml) and (29.6948 mg*hr2/ml) and mean residence time for caffeine was (34.12 mg*hr2/ml) by NCOMP and (29.6948 mg*hr2/ml) by equation, Table(1) and Figure (3).

Table 1. - Pharmacokinetic Parameters of Caffeine in Saliva.

Pharmacokinetic parameters	NCOMP Results	Calculation Results
Dose (mg)	200	200
Ke (hr^{-1})	0.69	0.69013
$T_{1/2}$ (hr)	1.00	1.0041
Vd (L\kg)	18.17	17.5265
Cl (L^{-1}\hr\kg)	10.32	12.0957
C_{max} (mg)	15.52	15.521
T_{max} (hr)	0.5	0.5
MRT (hr)	1.76	1.6131
AUC (mg*hr/ml)	16.49	18.408
AUMC (mg*hr^2/ml)	34.12	29.6948

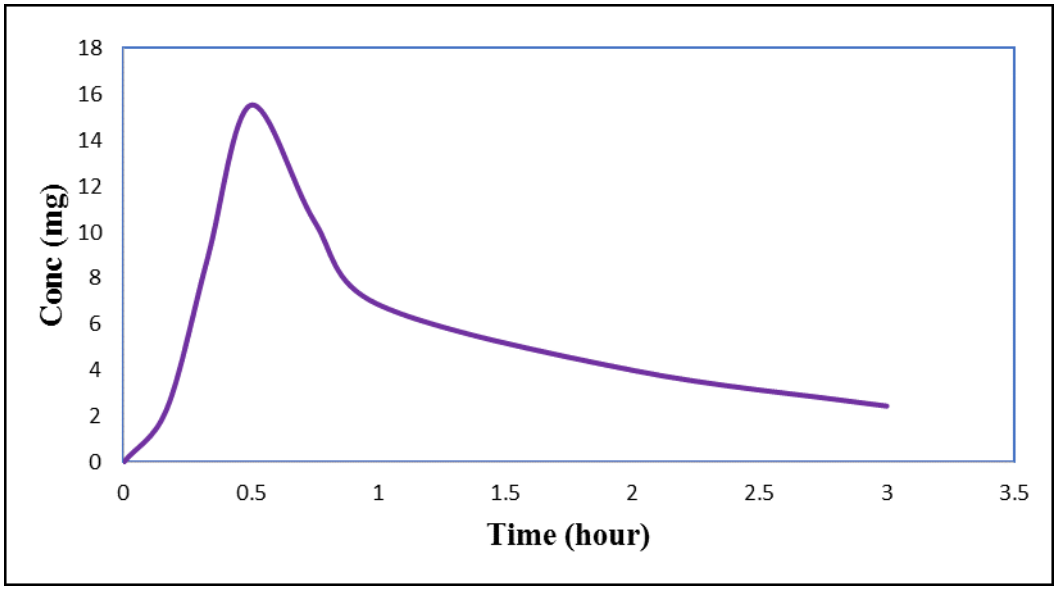

FIGURE 3. - Concentration versus Time Curve of Caffeine in Saliva

4. DISCUSSION

The pharmacokinetic study of caffeine from coffee that contains 200mg of caffeine per 100ml of coffee, as this study showed that caffeine half-life approach to one hour.

The present study is in agreement with (Nehlig, 2018) who mentioned that caffeine with its short half-life is rapidly and almost completely 99% absorbed from gastrointestinal tract about 20% of caffeine absorbed from the stomach and 80% from small intestine and such process is similar in most evaluated species. However, a significant role of oral mucosa in transmittance was also proved.

This research is disagreed with (Williams et al,2020) who said that caffeine half-life is 3–6hr. and (Evans and Battisti, 2019) who claimed that caffeine half-life is about 5 hours in the normal adult. However, their sample size and methodology is quite different from ours.

Alsabri et al., (2018) and Newton et al., (1981) said that caffeine is quickly distributed to most tissues and organs. The process is related to its plasma content, with a mean volume distribution of 0.6–1.06 l/kg.1. Distribution usually does not change during a person's entire life, but is significantly greater in women and obese individuals, in whom the value positively correlates with weight. The protein binding in both human and laboratory animals is relatively low and was estimated at 17–30%. Because alkaloid easily crosses intracellular barriers, including placental and blood–brain ones, it is well detectable in various body fluids (i.e., bile, milk, saliva, semen, sweat, and urine).

Brazier et al., (1983) mentioned that various experimental and human studies proved that caffeine is excreted mostly by kidneys. Caffeine clearance is highly dependent on renal blood flow and urine passage, because the alkaloid and dimethylxanthine (its primary metabolite) are strongly reabsorbed (98%) in nephron tubules, but the final urine concentration significantly correlates with the plasma caffeine level. Caffeine is also excreted into saliva and sweat.

This study is in agreement with (Bhola and Palta, 2020) which claimed that caffeine clearance approaches to 15 mins.

Chaabane et al., (2017) understood caffeine as a neutral lipophilic molecule that diffuses readily from the blood into the saliva, independent of flow rate and salivary pH, as several prior studies have validated the use of saliva to monitor caffeine concentrations.

Scott et al., (1984) found a great relationship was watched between the concentrations of caffeine in saliva and in blood proposing that salivary estimations may be valuable for the study of caffeine pharmacokinetics in man.

These results of Caffeine excreted in the saliva can has an effects on elevation of the pH of the saliva to reduce the harmful effect of acidity challenger and subsequent caries production specifically for orthodontic patients.

5. Conclusion:

Caffeine have an impact on the reduction acidity of the saliva as in this Caffeine pharmacokinetic study showed that caffeine excretes in saliva and has short half-life equal to one hr.

Funding

No funding received for this work

ACKNOWLEDGEMENT

We thanks the Collage of Dentistry University of Mosul for their support in conducting this research.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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