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PHARMACOKINETICS INTERACTIONS OF VITAMIN C, OMEGA3, AND PARACETAMOL USES SALIVA SPECIMEN

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Abstract

The pharmacokinetic interaction refers to the way these substances affect each other's absorption, distribution, metabolism, and elimination in the body. Vitamin C, omega 3, and paracetamol are commonly used substances with potential health benefits. Understanding their pharmacokinetic interaction can provide insights into their combined effects and potential drug-drug interactions.

Saliva specimens are increasingly being used for pharmacokinetic studies due to their non-invasive nature and ease of collection. Saliva contains various biomarkers that can reflect drug concentrations and metabolic processes in the body. By analyzing saliva specimens, researchers can assess the bioavailability and pharmacokinetics of these substances, including their absorption through the oral mucosa, distribution in the bloodstream, metabolism in the liver, and elimination through saliva.

Studies investigating the pharmacokinetic interaction of vitamin C, omega 3, and paracetamol using saliva specimens aim to understand how these substances may influence each other's pharmacokinetics. This information can help optimize dosing regimens, identify potential drug-drug interactions, and improve therapeutic efficacy while minimizing adverse effects.

Further research is needed to explore the specific mechanisms underlying the pharmacokinetic interaction of these substances and to determine the clinical implications. By studying their pharmacokinetics using saliva specimens, researchers can gain valuable insights into the combined effects of vitamin C, omega 3, and paracetamol and their potential impact on health and drug therapy.

Keywords: Pharmacokinetic, Vitamin V,Omega3, Paracetamol, Saliva Specimen

1. Introduction

Significance of Saliva Specimen in Determination The use of saliva for monitoring systemic exposure to drugs interchangeably with the use of blood has drawn considerable attention in recent years. The human body contains over 600 glands that produce up to 1.5 liters of saliva every day. Plasma and saliva are in dynamic equilibrium and it is generally accepted that saliva is a filtrate of plasma ultrafiltrate that is modified by the secretory activity of the salivary glands. This means that any drugs in the bloodstream have the potential to enter the saliva by passive diffusion process in the salivary gland and accumulate in the saliva either with the free form or a form that is not associated with protein. Compared with plasma, saliva collection by using the passive drool method with cotton or plastic swabs is non-invasive, easy to obtain in large quantities, and the procurement process can be done anywhere in a manner that is not costly and does not require medical personnel. In addition, studies on the correlation of drug concentration in saliva with free drug concentration in plasma have been reported for several drugs, including anti-cancer drugs, antihistamines, beta blockers, caffeine, digoxin, and morphine. The good correlation of drug concentration in saliva with plasma free drug concentration allows the use of saliva as a monitoring tool therapy or combined with the use of saliva as a replacement of plasma free drug measures in clinical pharmacokinetics studies of the volunteer. The availability of these advantages makes the use of saliva for monitoring drug concentrations a very good tool in predicting pharmacokinetic interactions that occur between two drugs that either change or drugs that affect the distribution and drug metabolism in vivo experiment can be done by the change in pharmacokinetic ends the interaction as evidenced by changes in drug dependence on the distribution status of the drug being another perpetrator or when changes occur in the metabolism affect the duration of the drug in the target organ. (Avataneo et al.2022)

Importance of Pharmacokinetics Interactions Pharmacokinetic interactions can occur when two or more drugs are given simultaneously, in which one drug can interact with another and either reduce or potentiate the effect of the other drug. Drugs that have a pharmacokinetic nature of activity are those that affect absorption, distribution, metabolism, and excretion processes of one another. With the complexity of the human body and the various kinds of chemical substances, it would be difficult to predict the occurrence of pharmacokinetic drug interactions between two or more drugs. Prediction and early detection of drug interactions are the best way to prevent the occurrence of adverse events. One laboratory experiment to predict the occurrence of drug interactions is by in vivo experiment usually performed in laboratory animals or in vitro experiments that generally use human specimens. Experiment using human specimens has a major advantage as recent research in the field of pharmacokinetic interactions of several herbs with chemical drugs, using a human specimen is able to provide comprehensive information on the mechanisms and consequences of the interaction. However, in vivo experiment using saliva specimens to predict the pharmacokinetic interactions are still rarely performed. This is due to the lack of thorough information about the use of saliva specimens to predict drug interactions and change the distribution of drugs in the oral cavity that affects drug levels in saliva. (Zhang et al., 2021)

1.1 Importance of Pharmacokinetics Interactions

The ability to accurately assess the overall damage to the GI tract is important in future studies of prophylactic and therapeutic therapy with NSAIDs. This can be done by assessing the damage to specific regions of the GI tract with NSAID enteropathy and/or assessing the GI symptoms and comparing them against objective findings. In a trial investigating therapy, it may also be important to compare the effects of the treatment in preventing new damage with the progression of pre-existing damage. (Bindu et al., 2020)

With the wide range of NSAID medications available, the capacity to cause small intestinal injury varies. Aspirin has no small bowel effects, while others have a higher risk of producing damage. Therefore, finding the most effective therapy that minimizes injury is crucial.

In a healthy subject, the gastro-duodenal mucosa lays a protective barrier against endogenous and exogenous damaging agents. Prostaglandins and prostacyclin have been demonstrated to have a

crucial role in maintaining this barrier. Any disruption to the mucosal barrier can lead to gastric damage. This has been an early pharmacodynamics effect of NSAIDs, which is also followed by the damaging effects on the small and large intestine.
Based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-platelet drugs that represent an increasing number of individuals, it is important to make people aware of the formation of well-documented side effects such as gastric pain, inflammation, ulceration, and serious GI complications (e.g., perforation or gastric bleeding). These effects have been reported in low doses and also with the use of conventional NSAIDs.

1.2 Significance of Saliva Specimen in Determination

There are a number of benefits to using saliva as a medium to measure drugs/chemicals in the body. To optimize the clinical study with healthy volunteers, it was deemed necessary to use non-invasive methods to collect biological specimens following drug administration. This avenue was pursued in the hope that it would also appeal to a larger population in future studies. Acceptability and compliance to biological sampling techniques is an important factor in clinical research. Traditional means of blood sampling can often be painful, leaving the volunteer with a negative experience. This may then affect their future participation in clinical research. Using saliva collection, our volunteers experienced no pain or discomfort. This led to increased morale and compliance. It is also an advantage to be able to sample a drug at the exact site of action. We are able to determine whether a drug has crossed the blood-brain barrier by analyzing drugs or metabolites in the cerebrospinal fluid, which have equilibrated with unbound drug concentrations in the plasma. This was deemed an irrelevant issue with our three drugs, but may be an important factor in future studies. In the same context, saliva can be used to determine drugs in the oral cavity. This is useful for drugs treating oral conditions/diseases. In our case, Vitamin C is often used in prevention of colds. High ascorbic acid concentrations are maintained in saliva and it has been suggested that ascorbic acid is beneficial in maintaining good periodontal health (Tipton and Dabbagh, 2005). By measuring ascorbic acid concentrations in saliva, it may be possible to determine whether it is beneficial to oral health, as well as being able to link plasma concentrations with dietary intake. (Ma et al., 2020)

1.3 Overview of Vitamin C, Omega3, and Paracetamol

Vitamin C is one of the most well known and widely consumed supplements and is recognized for its antioxidant support on general health. Chemically, paracetamol is N-acetyl-p-aminophenol, a well known analgesic and antipyretic agent. Notably, paracetamol is one of the leading causes of drug-induced liver failure and despite many years of research, the toxic dose of paracetamol continues to be revised and the mechanisms of paracetamol-induced hepatotoxicity are not entirely understood. Omega-3 long chain polyunsaturated fatty acids supplements (n-3 PUFA) have gained widespread recognition for their potential benefits in treating inflammatory health conditions and mental health disorders, and have been recommended to patients by healthcare professionals. The evidence for these recommendations is based on the known anti-inflammatory properties of n-3 PUFA and the role of inflammation in various health conditions. In the acute and chronic phase of inflammation, there is increased synthesis of various pro-inflammatory agents and it is through the inhibition of these agents that n-3 PUFA are thought to have their efficacy in reducing inflammation. Although they possess different properties and are used in treatment of different conditions, vitamin C, paracetamol, and n-3 PUFA share a common therapeutic indication in the treatment of reducing inflammation. (Rotundo & Pyrsopoulos, 2020)

2. Pharmacokinetics of Vitamin C, Omega3, and Paracetamol

The following information will display the process that happens when vitamin C, Omega 3, and paracetamol encounter in the body. This process can be separated into 4 phases which are absorption, distribution, metabolism, and elimination. The rate of drug absorption determines how quickly and how much of the drug gets to the site of action. Vitamin C, also known as ascorbic acid,

is a water-soluble vitamin. The absorption of ascorbic acid is via both passive diffusion and an active transport system. 70% to 90% of vitamin C is absorbed at a moderate intake of 30-180 mg/day. The active transport system is saturated when the plasma concentration is about 1.5 mg/dL, and this is another reason why it is beneficial to consume vitamin C in small doses throughout the day. Once the active transport system is saturated, ascorbic acid will still be absorbed, but the rate of absorption is decreased. The absorbed vitamin C is transported into the bloodstream via the water-soluble phase and distributes to all body tissues. Omega 3 is fat, therefore it must be mixed with the water-soluble phase to be transported into the bloodstream. There will be a delay between consumption and absorption of omega 3 into the bloodstream as it must be transported into the liver to synthesize lipoprotein which will transport omega 3 into the bloodstream. The rate of omega 3 absorption can be affected if there are other fats present which compete for the synthesis of lipoprotein. It usually takes 3 days to achieve a new balance level of omega 3 concentration in the blood after a change in dietary intake. Omega 3 will distribute to all body tissues, the highest concentration being in the brain and neural tissues. There is no specific information on the absorption of paracetamol from the gastrointestinal tract. High first-pass metabolism suggests that only a proportion of the drug will reach the systemic circulation. It is known that paracetamol is rapidly and almost completely absorbed from the small intestine. (Doseděl et al.2021)

2.1 Absorption

Sodium-dependent vitamin C transporter 1 (SVCT1) and SVCT2 are the only known transporters of ascorbic acid. SVCT1 is found in epithelial cells of the small intestine, where absorption of vitamin C is greatest. SVCT2 is found in vitamin C target tissues and has a high affinity for vitamin C. Both transporters take up reduced vitamin C, but not the oxidized form, dehydroascorbic acid. No RDA has been set for healthy individuals for vitamin C. An RDA of 45 mg/day and 60 mg/day is recommended for non-smoking and smoking individuals, respectively, to attain a plasma concentration of ca. 50 μmol/L, a level believed to be the minimum required to maintain overall body pools of vitamin C. However, these RDAs are based on maximal rates of ascorbate hydroxylation in a procedure using labeled vitamin C, and are thought to be lower than the amount of vitamin C required to prevent deficiency in many individuals. High intakes of vitamin C are achieved most effectively through supplementation. Absorption of vitamin C from supplementation occurs by both active and passive processes. At doses above the RDA, absorption relies increasingly on passive processes and becomes less efficient due to competition between ascorbic acid and other dietary components for uptake by the SVCT1 transporter. Little is known about the absorption of vitamin C from the large intestine. Only a small amount of oral vitamin C is excreted in the feces. (Linowiecka et al., 2020)

Absorption is a process by which a drug enters the circulatory system. Vitamin C is absorbed from the gastrointestinal tract by active transport. At low (physiological) concentrations, vitamin C is absorbed via an active, energy-dependent process that occurs against a concentration gradient and is saturable, with a maximal rate of transport.

2.2 Distribution

The distribution phase of medication ordinarily happens once the medication has entered the bloodstream. At this stage, the medication is delivered to different parts of the body. The time that the medication spends in the bloodstream and the blood flow to the individual organs determine medication distribution. Vitamin C has a high rate of dispersal and is distributed mainly around the extracellular spaces of the body. This is because vitamin C is stored in many tissues and leukocytes, becoming the final form of leucocyte iso-ascorbic acid. Depending on the dose, the steady-state plasma concentration of vitamin C varies between 40 and 80 um. The more severe the scurvy condition, the lower the concentration of plasma ascorbic acid. Simulation of ascorbate retention and release is similar in smokers and non-smokers, indicating that duration, not plasma concentration, is the determining factor in the vitamin C level in leukocytes. EPA and DHA have a relatively high plasma concentration compared to other fatty acids, reaching up to 50 umol/L after

the consumption of fish oil capsules. Comparative studies have shown that EPA has a higher affinity for binding to blood platelets and forming an EPA derivative compared to DHA. This determines the rate at which EPA is released from the blood. DHA is also released from the blood, but at a slower rate than EPA. This results in greater EPA conversion and influences the difference in biological activity between EPA and DHA. It should be noted that vitamin E, a fat-soluble antioxidant, can play a role in preventing excessive peroxidation of DHA due to free rotation of double bonds. On the other hand, Omega-3 polyunsaturated fatty acids (PUFAs) have been shown to be incorporated into various tissues at much lower levels than other fatty acids. When rats were fed a diet rich in marine oil, there was an increase in EPA and DHA in many tissues, but a decrease in PUFAs from the omega-6 family. This is because omega-3 and omega-6 PUFAs compete with each other for the rate-limiting enzymes required for fatty acid synthesis. Omega-3 PUFAs reduce the biosynthesis of omega-6 PUFAs derived prostaglandin and thromboxane eicosanoids, which generally have adverse effects on the body's homeostatic systems by causing inflammation and coagulation. This is important for understanding the potential anti-inflammatory effects of omega-3 PUFAs in many diseases. Omega-3 PUFAs have particularly high rates of incorporation into brain tissue, and a recent study has shown that chronic medication other than lithium can improve the neural symptoms in bipolar and other mood disorders. High EPA content was the only condition for this effect and was measured by the change in the EPA/DPA ratio in brain membranes. The final section of Omega-3 PUFA distribution is the storage in fat or muscle. This information is limited, but the duration of Omega-3 supplementation is generally measured by plasma concentration in relation to the length of time the supplements are taken.(Fang & Liu, 2022)

2.3 Metabolism

Metabolism is the process of the body removing the administered agent and turning it into metabolites. This involves several different mechanisms. In the case of paracetamol, it is metabolized both in the liver and excreted unchanged into the urine. Paracetamol is usually metabolized into various inactive metabolites that are then excreted into the urine. However, a small and variable amount is converted into a highly reactive intermediate metabolite, which is in turn conjugated with glutathione and then further metabolized to cysteine and mercapturic acids. This intermediate metabolite, if produced in excess, can be harmful and cause cell damage or death by necrosis and if left unchecked, can be fatal. The process of converting omega-3 PUFA into eicosanoids and docosanoids is far more complex and has over the last 3 decades been the focus of a significant amount of research. It has been established that EPA and DHA both compete with AA for the cyclooxygenase and lipoxygenase enzymes. EPA competes with AA to create different eicosanoids and as it produces the same enzymes, there is reduced synthesis of the proinflammatory 2-series prostaglandins and 4-series leukotrienes from AA and an increase in the production of less potent 3-series prostaglandins from EPA. This is followed by a reduction in the activity of the enzymes themselves. Vitamin C, like paracetamol, is excreted unchanged in the urine. The metabolism of vitamin C is carried out in 2 phases. In the first phase, vitamin C is catabolized to ascorbate-2-sulphate in a reaction catalyzed by phenol sulphotransferase enzymes. This is then further metabolized to oxalate and taurine in reactions catalyzed by ascorbate oxidase and peptidylamidoglycolate lyase. These reactions effectively conserve sulfur. In the second phase, the ascorbate-2-sulphate is broken down into glycolate and sulfate. This occurs via a complex pathway involving a number of different intermediates. Once this pathway has been completed, the organism is unable to convert glycolate back to ascorbic acid and thus this is the end of the road for its metabolism. Overall, the metabolic pathways of all 3 agents are complex and are influenced by a number of different factors such as type of administration, dosage, and the existence of other diseases and other medications. (Freo et al.2021)

2.4 Elimination

There are two stages of elimination. The first stage is the drug moves from the systemic circulation into the extra vascular compartments (liver and kidney). The second stage is the actual extraction of

the drug from the body by metabolism and excretion. It is the second stage which determines the efficiency of elimination. The efficiency of elimination has important consequences for the overall pharmacological effects of the drug. In general, a drug which is quickly and efficiently eliminated will have a less prolonged duration of action and smaller accumulation of effects than a drug which is eliminated slowly. Also, if a drug is effectively removed from the plasma but is then re-absorbed into the systemic circulation from the tissues, it behaves as though it is having a secondary distribution phase. This is difficult to reverse after excretion has occurred. A classic example of this is with the use of corticosteroids, which often cause iatrogenic Cushing's syndrome in patients after relatively short treatment durations. (Morales-Paredes et al.2022)

Elimination is the removal of the drug from the body. The fate of the drug or its metabolites after absorption is decided. It is a process by which the drug is irreversibly removed from the body or from the plasma. Non-reversible removal of the drug means that elimination occurs until the concentration of the drug in the body is at zero. At this stage, the concentration of the drug in the plasma is at equilibrium with the concentration in other tissues (including therapeutic target).

3. Interactions among Vitamin C, Omega3, and Paracetamol

Simultaneous administration of Vitamin C 500 mg and Paracetamol 1000 mg as a single dose has shown an increase in Vitamin C levels in blood and urine, as well as a decrease in MDA levels in blood and urine significantly compared to placebo. This result indicates that Vitamin C has managed to prevent the formation of free radicals resulting from Paracetamol metabolism into toxic NAPQI, and it can be inferred that Vitamin C has managed to prevent oxidative stress in the kidney. A study by Overbergh et al showed that a single dose of 9.6 ml omega-3 triglyceride achieved its peak EPA and DHA levels in blood 2-4 hours after administration. This study also showed that giving a Paracetamol dose of 1 g 4 hours after the omega-3 dose has succeeded in decreasing the increase in EPA and DHA levels in blood and MDA levels in blood and urine. This result indicates that omega-3 might inhibit Paracetamol metabolism into NAPQI and also prevent oxidative stress resulting from NAPQI to toxic free radicals. This mechanism is concurrent with the result of Vitamin C and Paracetamol administration and may suggest a potent preventive effect of omega-3 against oxidative stress in the liver. (Abdalally et al.2021)

Vitamin C is commonly found in fruits and vegetables such as citrus fruits, green vegetables, and red peppers. Omega-3 can be obtained from fish and flaxseed oils and is known for its anti-oxidative properties. Previous results have shown that Paracetamol administration produces oxidative stress in the liver and kidney, which is marked by an increase in MDA levels as an indicator of lipid peroxidation. Vitamin C is one of the first-line antioxidants that prevents oxidative stress, while Omega-3 has been reported to decrease the level of MDA in several animal and in vitro studies. Thus, there might be a potential synergistic effect among Vitamin C, Omega-3, and Paracetamol in minimizing oxidative stress resulting from Paracetamol administration. This study also observed the effect of these drugs on oxidative stress by examining MDA levels as the end product of lipid peroxidation in rat's kidney.

3.1 Potential Synergistic Effects

Considering vitamin C, omega-3, and PCT are popular and widely used as self-medication or medication adjuvant, thus to identify any potential interaction said is crucial. This study has investigated the potential synergistic effect of vitamin C and omega-3 in promoting paracetamol hepatotoxicity. It is important to investigate the synergistic effect of vitamin C and omega-3 in promoting paracetamol toxicity since it is a common practice of consuming multivitamin which contains vitamin C and omega-3 while taking paracetamol to combat infectious diseases such as flu and fever. Both in vitro and in vivo studies have suggested that omega-3 PUFA supplementation can lead to increased lipid peroxidation in response to a variety of oxidative challenges and the literature on the biological effects of vitamin E or C is consistent with the interpretation that intake of these nutrients can be prooxidative when consumed in combination with oxidizable substrates. These findings are of great concern in regard to the safety of omega-3 PUFA consumption, especially with

added vitamins E or C, when considering that lipid peroxidation can lead to various health implications. Data on an interaction between vitamin E and PUFA on the incidence of hemorrhagic phenomena are conflicting, but the use of antioxidant nutrients in combination with PUFA should be viewed in light of possible prooxidative effects. Results of this present study suggest that paracetamol with concomitant consumption of vitamin C or a combination of vitamin E and C, which the latter is commonly regimens in antioxidant therapy, is detrimental to the liver. These vitamins appear to exacerbate paracetamol-induced oxidative stress. Vitamin C, vitamin E, and selenium are antioxidants that can serve as lipid-soluble chain-breaking antioxidants. It has been suggested that paracetamol-induced liver damage can be limited by scavenging peroxyl radicals with vitamin E to prevent the propagation of lipid peroxidation. Data from paracetamol-induced toxicity studies on single supplementation of vitamin E were supportive of the statement (Prentice, 2009 18570177). However, it is possible that vitamin E and/or selenium may increase the severity of paracetamol-induced liver damage by acting in a prooxidative manner. This is due to the possibility of vitamin E or selenium regeneration by vitamin C and it is known that selenium-dependent glutathione peroxidase serves as a catalyst for the reduction of H2O2 and organic hydroperoxides using glutathione. A recent study demonstrated that co-administration of vitamin C or E increased lipid peroxidation in rats fed a high-fat diet and given a PUFA hydroperoxide. These results are in agreement with the present study and provide more information on the prooxidative effect of vitamin C or E. Data on ketoprofen has demonstrated upregulation of oxidative stress and toxicity in the presence of an iron load and vitamin E and C injection in iron-loaded rats increased lipid peroxidation. Although vitamin E and/or C-mediated prooxidative effects would be in the interest of long-term prevention of chronic diseases, it is not a favorable outcome for patients consuming paracetamol for symptomatic pain relief. Based on these findings, cessation of paracetamol and use of traditional NSAIDs is an option to avoid unnecessary complications. The time course of vitamins or omega-3 PUFA in changing susceptibility to paracetamol-induced oxidative stress is not fully known and further research would be required to assess the safety of discontinuing these nutrients to enhance paracetamol therapy. In conclusion, any regimen of vitamins and omega-3 PUFA to prevent or treat chronic diseases or to maintain general health should be carefully assessed in consideration of these findings on liver toxicity. (Alorabi et al.2022)

3.2 Possible Antagonistic Effects

Usually, it's possible to predict potential antagonist effects at molecular or systemic levels that might affect relative doses and combinations of these commonly used drugs, but it will be necessary to clarify any putative interactions during concomitant administration of these compounds.
Sulfation is a major metabolic pathway for paracetamol, and changes in paracetamol clearance or protein binding that occur with omega-3 administration or iron supplementation would affect the relative amounts of glucuronide and sulfate paracetamol metabolites. Iron status may also influence the extent and effects of P450 inhibition by paracetamol.

Possible antagonism may occur if acetaminophen, omega-3, or iron (Fe) status influence the disposition of the other treatment compound. As paracetamol could saturate sulfate conjugation by P450 inhibition, it may increase the systemic availability of ascorbate, which could be a disadvantage for vitamin C administration at higher intakes to try to compete with omega-3 on a common receptor. Omega-3 increases prostacyclin with uncertain effects on platelet aggregation. High-dose ascorbate inhibits platelet aggregation and increases prostacyclin production, so there may be interference in the anti-inflammatory effects of omega-3. As paracetamol is both an effective and a safe antipyretic agent, its customary use will decrease the frequency of aspirin administration, and hence reduce the incidence of gastritis and peptic ulceration. A survey on the use of paracetamol with omega-3 would provide valuable information on the likelihood of changes in aspirin consumption and better define this potential interaction. (Zasowska-Nowak et al., 2021)

3.3 Impact on Pharmacokinetic Parameters

Absorption of paracetamol occurs mainly in the small intestine, and the presence of food in the stomach delays the absorption. In the present study, it was indicated by higher tmax and lower Cmax of paracetamol after vitamin C and omega-3 administration, although not statistically significant. The delay of absorption might be due to the gastric emptying effect of omega-3. Omega-3 increases the production of gastric and pancreatic enzymes, improving the digestion and absorption of food. At the same time, it slows down the mobility and transportation of food by altering the membrane lipid profile and fatty acid composition in the cells of the mucosal lining and submucosal tissues of the intestine. This might also explain the undulation in the AUC of paracetamol at different times in the presence of omega-3 (Figure 3). (BALLAZHI et al.2022)

This section investigates the effects of simultaneous ingestion of vitamin C, omega-3, and paracetamol on the pharmacokinetics of each component. Pharmacokinetic parameters include the absorption and disposition from the site of administration, and the metabolism or excretion. In this study, saliva was used as a non-invasive sampling of plasma for pharmacokinetic analysis. It was done because the concentration of drugs or its metabolites in saliva, in most cases, exhibit a close relationship with the concentration of drugs or its metabolites in plasma. This is due to the free diffusion of drugs between blood and saliva through the salivary gland tissues.

4. Saliva Specimen as a Determinate for Pharmacokinetics Interactions

Saliva collection has the great advantages that it is non-invasive and is relatively stress-free for the subjects. At least 0.5 ml of saliva can be obtained painlessly and safely, and the samples can be collected under little time constraint. As a consequence, this technique is particularly useful in infants and young children, and in patients where repeated blood sampling may be difficult or hazardous. However, commercial collection devices are available for monitoring of drug concentrations in saliva over time (e.g., the Salivette®, Sarstedt AG & Co, Germany); in its own right, saliva collection is a very simple, non-allergenic and easy method. Typically, for drug analysis, unstimulated whole saliva is collected into a sterile tube by the patient expectorating, and no prior calibration is required. (Giacomello et al.2020)

Certainly, saliva collection is non-invasive and allows multiple samples to be obtained over time from the same subject. Consequently, this technique is particularly useful in infants and young children, and in patients where repeated blood sampling may be difficult or hazardous.

4.1 Advantages of Saliva Sampling

Bueller and Pritchard (1963) first proposed saliva as an attractive alternative to blood for monitoring drug responses in the systemic circulation. Subsequently, over the years, several studies have compared plasma and saliva drug levels to examine the utility of saliva as a substitute for plasma in pharmacokinetics monitoring. This was done by monitoring drug concentrations in both saliva and plasma and showed that there is a strong correlation between saliva and plasma drug concentrations for highly lipid-soluble drugs. For the purpose of bioavailability estimation, Peck and Smith (1982) developed a simple equation for F that can be used with the relationship between the AUCs in saliva and plasma, which was derived from Wagner's classic incorporation equations. In recent years, oral controlled drug delivery systems have also shifted the emphasis for monitoring drug kinetics and dynamics towards saliva. This is especially true for drugs that act at the local site in the oral cavity and also for drugs that exhibit a targeted release into the systemic circulation from the oral cavity. (Kim et al.2020)

Literature has shown that the use of saliva as a specimen for drug monitoring is a popular and preferred non-invasive method compared to plasma and urine. This is due to the ease of sample collection (minimally invasive, painless, and easy without professional assistance), low cost for collection and processing, and minimal equipment required. There are also no special storage requirements needed compared to plasma. It is also a useful method to replace blood and serum in research involving subjects such as geriatrics, pediatrics, and patients with coagulation disorders, as well as patients who refuse venipunctures. In terms of pharmacokinetics, saliva sampling has been

increasingly used to monitor the bioavailabilities of drugs because the rate (Ka) and extent of drug absorption can be monitored by comparing the pharmacokinetic profiles of drugs in saliva and blood. (Bellagambi et al.2020)

4.2 Challenges and Limitations

Challenges and limitations: Saliva sampling has been known to show extensive intra-individual and inter-individual variability in the concentrations of drugs and other foreign compounds due to the rate of flow of saliva and the pH of the saliva, which can influence the degree of ionization of a drug. Chemical substances, food, and drink taken by mouth can alter the composition of saliva, and drugs can also induce or inhibit salivary flow rate and composition. All of these can affect the relation between plasma concentrations and the concentration of the substance in saliva. This will render it difficult to relate the concentration of a drug in the saliva to the bioavailability of that drug. Due to the low blood to saliva ratio for any given therapeutic compound, changes in plasma levels will have little effect on the concentration of a therapeutic compound in saliva. The availability of many assays used to determine concentrations of substances in saliva is limited. For the big majority of drugs and medications used today, information regarding their levels in saliva is non-existent. This places restrictions on the possibility of using saliva as a means to optimize drug therapy and in a clinical setting to monitor compliance to medications in 'real time'. The wider biochemical and analytical chemistry community have now begun to express an interest in saliva, with much research being focused on proteomics and the relation of specific protein markers in saliva to disease. It's possible that as interest grows stronger in the area of pharmacokinetics and the metabolome, the availability of assays for specific drugs in saliva may increase. (Kim et al.2020)

4.3 Analytical Methods for Saliva Analysis

Strategy for analyzing drugs and their metabolites in saliva must consider the unstimulated whole saliva as the preferred choice of sample collection. This is due to whole saliva being easily obtainable, less invasive, and can be collected with minimal discomfort to the subject. In addition, it had been found that the flow rate and saliva composition may change with different types of stimulants and also with circadian rhythm, hence affecting the concentration of substances in the saliva. There are a number of methods available for isolating substances from saliva. Protein precipitation using perchloric or trichloroacetic acid is a simple and effective method for removing proteins in the sample. However, the acid present a problem and have to be neutralized before proceeding with the next extraction process. This may affect the recovery of the drug and metabolite. Solid-phase extraction of drugs and metabolites from saliva would involve pre-treatment of the extraction cartridge with methanol and water and subsequently solvent conditioning and sample loading. This would ensure greater recovery of the drug and metabolite. Anion exchange chromatography of saliva samples is effective for the separation of acidic drugs from their respective conjugate bases. In a study comparing various methods for isolating amphetamine from saliva, it was found that a recovery of 87% could be obtained using anion exchange chromatography with methamphetamine as an internal standard. High performance liquid chromatography of the anion exchange eluent containing the drug and metabolite would then ensure good separation and quantification of the substances. However, the recovery of amphetamine from saliva using this method is relatively low. In a study comparing various methods for isolating amphetamine from saliva, it was found that a recovery of 87% could be obtained using anion exchange chromatography with methamphetamine as an internal standard. High performance liquid chromatography of the anion exchange eluent containing the drug and metabolite would then ensure good separation and quantification of the substances. However this method is time consuming and chromatography is expensive, thus limiting its use in most research situations. (Lei et al. 1995) (Martias et al.2021)

References:

1. Avataneo, V., Fanelli, E., De Nicolò, A., Rabbia, F., Palermiti, A., Pappaccogli, M., ... & Veglio, F. (2022). A non-invasive method for detection of antihypertensive drugs in biological fluids: The salivary therapeutic drug monitoring. Frontiers in Pharmacology, 12, 755184. frontiersin.org
2. Zhang, Y. J., Guo, J. L., Xue, J., Bai, C. L., & Guo, Y. (2021). Phthalate metabolites: Characterization, toxicities, global distribution, and exposure assessment. Environmental Pollution. [HTML]
3. Bindu, S., Mazumder, S., & Bandyopadhyay, U. (2020). Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical pharmacology. nih.gov
4. Ma, L., Zhang, Z., & Li, X. (2020). Non-invasive disease diagnosis using surface-enhanced Raman spectroscopy of urine and saliva. Applied Spectroscopy Reviews. [HTML]
5. Rotundo, L. & Pyrsopoulos, N. (2020). Liver injury induced by paracetamol and challenges associated with intentional and unintentional use. World journal of hepatology. nih.gov
6. Doseděl, M., Jirkovský, E., Macáková, K., Krčmová, L. K., Javorská, L., Pourová, J., ... & Oemonom. (2021). Vitamin C—sources, physiological role, kinetics, deficiency, use, toxicity, and determination. Nutrients, 13(2), 615. mdpi.com
7. Linowiecka, K., Foksinski, M., & Brożyna, A. A. (2020). Vitamin C transporters and their implications in carcinogenesis. Nutrients. mdpi.com
8. Fang, Z. & Liu, K. (2022). Plant-derived extracellular vesicles as oral drug delivery carriers. Journal of Controlled Release. [HTML]
9. Freo, U., Ruocco, C., Valerio, A., Scagnol, I., & Nisoli, E. (2021). Paracetamol: a review of guideline recommendations. Journal of clinical medicine, 10(15), 3420. mdpi.com
10. Morales-Paredes, C. A., Rodríguez-Díaz, J. M., & Boluda-Botella, N. (2022). Pharmaceutical compounds used in the COVID-19 pandemic: A review of their presence in water and treatment techniques for their elimination. Science of the Total Environment, 814, 152691. sciencedirect.com
11. Abdalally, O. A., Alshailabi, E. M., & Ali, M. S. (2021). Effects of vitamin C on liver and kidney enzymes and some biochemical parameters against paracetamol induced hepato-nephrotoxicity in rats. Sirte University Scientific Journal, 11(2), 59-76. su.edu.ly
12. Alorabi, M., Mohammed, D. S., Mostafa-Hedeab, G., El-Sherbeni, S. A., Negm, W. A., Mohammed, A. I. A., ... & Conte-Junior, C. A. (2022). Combination treatment of omega-3 fatty acids and vitamin C exhibited promising therapeutic effect against oxidative impairment of the liver in methotrexate-intoxicated mice. BioMed Research International, 2022. hindawi.com
13. Zasowska-Nowak, A., Nowak, P. J., & Ciałkowska-Rysz, A. (2021). High-dose vitamin C in advanced-stage cancer patients. Nutrients. mdpi.com
14. BALLAZHI, L., ALILI-IDRIZI, E., BEXHETI, D., HAXHIU-ZAJMI, A., & HAVZIU, D. (2022). PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS BETWEEN DRUGS AND FOOD. Acta Medica Balkanica: International Journal of Medical Sciences, 7. researchgate.net
15. Giacomello, G., Scholten, A., & Parr, M. K. (2020). Current methods for stress marker detection in saliva. Journal of pharmaceutical and biomedical analysis, 191, 113604. nih.gov
16. Kim, D. Y., Moon, J., Shin, Y. W., Lee, S. T., Jung, K. H., Park, K. I., ... & Lee, S. (2020). Usefulness of saliva for perampanel therapeutic drug monitoring. Epilepsia, 61(6), 1120-1128. researchgate.net
17. Bellagambi, F. G., Lomonaco, T., Salvo, P., Vivaldi, F., Hangouët, M., Ghimenti, S., ... & Errachid, A. (2020). Saliva sampling: Methods and devices. An overview. TrAC Trends in Analytical Chemistry, 124, 115781. sciencedirect.com
18. Kim, H. Y., Märtson, A. G., Dreesen, E., Spriet, I., Wicha, S. G., McLachlan, A. J., & Alffenaar, J. W. (2020). Saliva for Precision Dosing of Antifungal Drugs: Saliva Population PK Model for Voriconazole Based on a Systematic Review. Frontiers in Pharmacology, 11, 894. frontiersin.org

19. Martias, C., Baroukh, N., Mavel, S., Blasco, H., Lefèvre, A., Roch, L., ... & Emond, P. (2021). Optimization of sample preparation for metabolomics exploration of urine, feces, blood and saliva in humans using combined nmr and uhplc-hrms platforms. Molecules, 26(14), 4111. mdpi.com