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Original Article

Serum and Saliva Theophylline Levels in Adult Outpatients with Asthma and Chronic Obstructive Pulmonary Disease (COPD): A Cross-Sectional Study

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Abstract

Due to a narrow therapeutic range, measurment of theophylline serum levels is highly recommended in patients with a long-term theophylline therapy. In this regard, since blood sampling is an invasive method, exploring alternative methods using other biological fluids in particular saliva samples are targeted. This study was designed to determine any relationship between serum and saliva levels of theophylline in patients with asthma and COPD, whom have been under xanthine–therapy for an extended period of time. Also, any relationship between serum or saliva levels of theophylline with possible explanatory factors was investigated. Adult (≥18 years) outpatients with a history of theophylline use (for at least 1 month) entered this study. Serum and stimulated saliva samples obtained 1 h before the morning dose and were measured using a high performance liquid chromatography (HPLC) method. To stimulate saliva production, patients chewed a piece of parafilm for 5 min before sampling. Relevant demographic information, medical and medication histories of the patients were also recorded. Collected data were entered into the SPSS (Statistical Package for Social Scientists, version 11.5) software and analyzed using the appropriate statistical tests ($p<0.05$). Eighty-six patients (44 males and 42 females) with a mean±SD age of 58.72±14.23 years enrolled in the study. Mean±SD of serum and saliva concentrations of theophylline were 5.4±2.8 mcg/ml and 4.0±2.1 mcg/ml, respectively. Forty five patients (52.3%) had subtherapeutic serum levels of less than 5 mcg/ml. There was a significant direct relationship between serum and saliva levels of theophylline ($p=0.0001$, $r=0.91$). Multivariate analysis led to a model in which only total daily dose of theophylline (mg) could remain as a predictor associated with the serum ($p=0.0002$, $r=0.53$) and saliva levels ($p=0.0001$, $r=0.47$). A considerable association observed between serum and saliva levels of theophylline, confirms previous reports. The observed high frequency of the patients with subtherapeutic serum levels emphasizes the importance of implementing therapeutic drug monitoring (TDM) of theophylline in patients with a long-term theophylline therapy, using non-invasive alternative sampling methods e.g. saliva sampling.

Keywords: Theophylline; Serum; Saliva; COPD; Asthma; Outpatients.

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Introduction

Theophylline and its ethylene diamine salt, aminophylline, have bronchodilator properties and are used in the treatment of asthma and COPD. In addition, theophylline has been shown to have some anti-inflammatory activities, inhibiting the activity of CD4 lymphocytes in-vitro and mediator release from mast cells. It can also inhibit bronchoconstriction produced by exercise and challenge testing. Theophylline has also been shown to have beneficial effects on contraction of diaphragm, an effect which may be particularly useful in patients with COPD (1, 2).

Although a rough guide to total daily dosage is 10-15 mg/kg in adults (higher in children) in 2 divided doses for sustained release preparations, the inter-individual variation in metabolism of theophylline, age, liver disease, heart failure and the effect of smoking, drugs, infection and fever can complicate the estimation of daily dose in an individual patient (2, 3). As plasma levels exceed 15 mg/l (normal therapeutic range 10-20 mg/l), the frequency of side effects also increases. The most common side effect is sinus tachycardia, nausea, tremor and indigestion. Deaths associated with theophylline toxicity have been reported. These may be due to cardiac toxicity, leading to life threatening dysrrhythmias, or associated with neurotoxicity. The mortality from theophylline related seizures approaches 30 percent (2, 4, 5).

Due to a narrow therapeutic range, measurement of theophylline serum levels is recommended in patients under long-term theophylline therapy. Since blood sampling is an invasive method, exploring alternative methods using other biological fluids, in particular saliva samples, are targeted. Being readily accessible and collectible, saliva can have many advantages compared to 'classical' biological fluids such as blood and urine. Researchers interested in the determination of drug concentrations have suggested that saliva might be substituted for plasma in the areas of pharmacokinetic studies and drug monitoring. In this regard, drugs like quinidine, lithium, phenytoin, carbamazepine, caffeine, ethanol, diazepam, phenobarbital, acetaminophen, cyclosporine, digoxin and theophylline were tried (6). Although, Zhai *et al* (7), Kirk *et al* (8), Blanchard *et al* (9), Virchow *et al* (10) and Williams *et al* (11) have confirmed a significant association between serum and saliva levels of theophylline, however, on the basis of current literature data, no comprehensive conclusion has been achieved.

The present study was designed to determine any relationship between serum and saliva levels of theophylline in real patients with asthma and COPD, who are under xanthine–therapy for an extended period of time. Also, the existence of any relationship between serum and saliva levels of theophylline with possible explanatory factors was investigated.

Experimental

Methods

This investigation was a cross-sectional study in which adult (≥18 years) outpatients with COPD or asthma, whom have been receiving long-term theophylline therapy (for at least 1 month), entered the study. All patients were on a generic preparation of theophylline (sustained release tablets) manufactured by an Iraninan pharmaceutical company. Patients referred to the respiratory clinic of the Shaheed Labbafinezhad teaching hospital, Tehran, Iran, enrolled the study using a non-probability sampling method. Patients did not have any concurrent renal or hepatic disorder, confirmed by diagnostic laboratory tests of ALT, AST, ALP, bilirubin, BUN and creatinine.

Serum and stimulated saliva samples obtained 1 h prior to the morning dose of theophylline. To stimulate saliva production, patients chewed a small piece of parafilm (5×5 cm, 0.3 g, Parafilm "M") for 5 min. Before collection, all the subjects rinsed their mouth with tap water. Saliva was allowed to accumulate on the floor of the mouth and the subjects were instructed to spit into a disposable plastic cup every 30 seconds. Subsequently, 10 ml of blood samples were collected in heparinated glass tubes. These samples were centrifuged and the obtained serum was used for theophylline determination. Theophylline concentrations were measured using a high performance liquid chromatography method (Knauer HPLC: K-1500 mixing chamber, K-1001 high pressure

Table 1. Studied possible explanatory factors related to the serum and saliva levels of theophylline.

Variable	Distribution
Age (year)	58.72±14.23
Gender	M=44, F=42
BMI	28.70±6.11
Height (cm)	159.87±8.91
Weight (Kg)	73.21±15.50
History of Asthma/COPD (years)	9.67±9.06
Theophylline dosage form	Tablet SR:76; Elixir: 10
Daily dose (mg)	284.88±121.81
Number of times theophylline is taken (per day)	1.66±0.63
Concurrent diseases (comorbidity)	Yes: 21; No: 65
Concurrent drugs	Increasing theophylline conc.: 42 Decreasing theophylline conc.: 0
Number of drugs taken by patients	4.99±2.16
Smoking habit	Smoker: 11; non-smoker: 75
Compliance score	4.15±0.86

Mean±SD; M: Male; F: Female; BMI: Body Mass Index; SR: Sustained Release.

pump, K-2600 Ultraviolet detector and Knauer Lichrosorb-100 C18 column) (12). Intra-day and inter-day reproducibility testing showed coefficient of variations of <5% and <7% for serum and saliva concentrations, respectively. Relevant demographic information, medical and medication histories of the patients were also recorded (Table 1). Patients' compliance were assessed using a questionnaire consisting of 4 simple questions (Table 2). Collected data was entered into the SPSS (Statistical Package for Social Scientists, version 11.5) software and analyzed using the Mann-Whithney U and Kruskal-Wallis H tests, rank correlations and the ridge regression analyses.

Results and Discussion

Ninety two patients enrolled this study, of them 6 patients were excluded due to a history of hepatitis (1 patient), increased levels of liver functional enzymes (4 patients) and renal failure (1 patient). Overall, 86 patients (44 males and 42 females) with a mean±SD age of 58.72±14.23 years entered the study. None of them had any renal or hepatic insufficiency, confirmed by BUN (12.74±4.33 mg/dl), Cr (0.99±0.19 mg/dl), ALT (19.26±10.82 U/l), AST (20.91±7.80 U/l) and Bil (Total: 0.56±0.22 mg/dl; Direct: 0.22±0.09 mg/dl) deteminations and medical history. Mean±SD of serum and saliva concentrations of theophylline were 5.4±2.8 mcg/ml and 4.0±2.1 mcg/ml, respectively. Spearman's rank correlation analysis revealed that there is a significant direct relationship between serum and saliva concentrations of theophylline ($p=0.0001$, $r=0.91$) (Figure 1). The equation describing this relationship is as follows (equation 1):

"$\boldsymbol{Serum\ concentration = 0.45 + (1.23 \times Saliva\ concentration)}$" **(equation 1)**

This model reveals a linear relationship between serum and saliva concentrations of theophylline , as showen in Figure 1.

Multivariate ridge regression analysis led to a model in which only total daily dose of theophylline (mg) could remain as a predictor associated with the serum ($p=0.0002$, $r=0.53$) and saliva levels ($p=0.0001$, $r=0.47$) of theophylline.

Forty five patients (52.3%) had subtherapeutic serum levels of less than 5 mcg/ml and only one patient (1.2%) had a serum level of 16.97 mcg/ml (higher than 15 mcg/ml).

Drugs such as theophylline, which are taken as long-term therapy and have a narrow therapeutic range, need frequent monitoring and

Table 2. Questionnaire designed to assess patients' compliance (minimum:0; maximum: 7).

Q1. Do you take your daily theophylline regularly?

always □ most times □ sometimes □ never □

Q2. Have you taken your theophylline in the past 3 days?

yes □ no □

Q3. Can you recognize the theophylline from other medications you take?

yes □ no □

Q4. Do you know what is the role of theophylline in your disease? (Name if the answer is yes)

yes □ no □

are good candidates for oral fluid assays. From the results obtained in this study it is concluded that theophylline concentrations in saliva may be useful in predicting serum values and this is in accordance with the results reported in previous studies. Chereches-Panta *et al* (13) showed that there is a strong correlation between serum and saliva concentrations of theophylline in infants with prematurity apnoea. Kirk *et al* (8) have also concluded that saliva concentrations could provide an adequate reliability for therapeutic drug monitoring of theophylline. However, since our present knowledge of saliva is incomplete, before a useful model describing salivary secretion of a drug such as theophylline can be applied routinely, one needs to know the predictability of the model obtained in this study. In addition, advanced knowledge about the mechanisms by which drugs enter the saliva, the effect of salivary flow rate and saliva pH as well as the protein binding of drug in the saliva have to be clarified more sufficiently. Drugs such as theophylline, phenytoin and carbamazepine which are not ionizable or are un-ionised within the salivary pH range are good candidates for salivary therapeutic drug monitoring (14), however, further studies are necessary to confirm these findings.

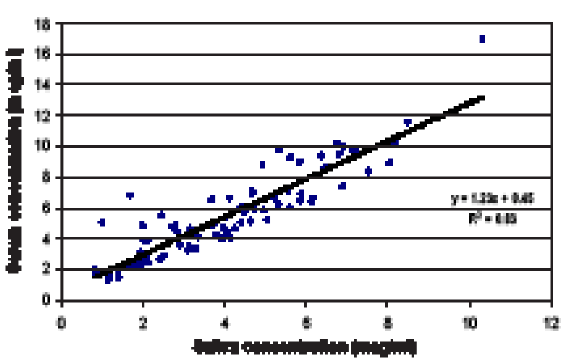

Figure 1. Relationship between serum and saliva levels of theophylline.

Though, factors including age, smoking habit and concurrent drugs (15) may affect serum and consequently saliva levels of theophylline, nevertheless, according to our findings only the total daily dose of theophylline was the predominant factor associated with the serum and saliva concentrations of the drug.

We found that more than 50% of the patients had subtherapeutic serum levels of theophylline. Similarly, Emerman *et al.* (16) in an study on patients with COPD obsereved that 47% of the patients (n=79) have subtherapeutic levels. Also, Ashkenazi *et al* (17) reported a subtherapeutic level of theophylline in 88% of asthmatic children (n=50). These findings emphasize the importance of regular therapeutic drug monitoring (TDM) of theophylline in outpatients with a long-term theophylline therapy.

More studies are needed to investigate confounding factors affecting the relationship between serum and saliva levels of drugs.

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