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SHORT COMMUNICATION

A Drug Utilization Research on Aminophylline/ Theophylline in Ali-Asghar Hospital, Shiraz, Southern Iran

S Namazi[1]*, Gh Vessal[1], Sh Hooshmand[2], MA Ostovan[3], Z Mehrpuor[1]

[1]Department of Clinical Pharmacy, School of Pharmacy, [2]Department of Internal Medicine, [3]Department of Cardiology, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Background: Drug utilization research (DUR) is an effective program to identify variability in drug use and to support interventions that will improve patient outcomes. The appropriate use of aminophylline/theophylline was evaluated in Shiraz, southern Iran.

Methods: A prospective DUR study was conducted in Ali-Asghar Hospital from April 2005 to April 2007. All inpatient cases of asthma or COPD who were started on IV loading dose of aminophylline were included in the study. A blood sample was provided from the patients at steady state condition just before the next dose, in order to determine the trough serum concentration of the drug. Demographic characteristics of patients, along with clinical and paraclinical findings, lab data, drug history, and adverse drug events were recorded using their files and a face to face interview.

Results: One hundred patients were enrolled among them, 57% (n=57) were female and 43% (n=43) were male. The age range was 16-90 years with mean age±SD of 65.63±14.7.

Diagnosis was asthma in 46% and COPD in 54% of patients. Theophylline serum concentration range was 0-37 mcg/ml (7.94±5.4). Ninety eight percent of patients had at least one adverse event due to aminophyline or theophylline use. 14 items were evaluated for aminophylline/theophyline administration and compared to a standard guideline. The mean score for 100 patients included in the study was 8 out of 14.

Conclusions: The most considerable problem in aminophylline/theophylline usage in our hospital was ignorance to the important role of pharmacokinetics in optimizing aminophylline/theophylline therapeutic response and minimizing ADEs and the cost of hospitalization. Training of the healthcare providers is recommended. Performing population pharmacokinetic studies will be a good guidance for improving aminophylline/theophylline usage in our population.

Keywords: Amionophylline; Theophylline; Serum concentration; Drug utilization research

Introduction

Drug utilization research (DUR) is an essential part of pharmacoepidemiology as it describes the extent, nature, and determinants of dug exposure. DUR and pharmacoepidemiology may provide insight into aspects of drug use and prescribing such as patterns of use, quality, determinants and outcomes.[1,2]

Theophylline is a highly toxic drug with a narrow therapeutic index and marked intersubject variability in pharmacokinetics.[3] Therefore a DUR study on theophylline would provide a strategy for optimizing theophylline use. There are many published studies regarding the evaluation of the management protocol for asthma and COPD,[4-6] but on the best of our knowledge, there was no DUR published for this drug. This study was conducted to evaluate the indication, administration, dosage, adverse drug events (ADEs), and therapeutic drug monitoring (TDM) of amino-

***Correspondence:** Soha Namazi, PhD, Assistant Professor of Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran. Tel: +98-711-2424127, Fax: +98-711-2424126,e-mail: sohanamazi@yahoo.com

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phylline/theophylline in hospitalized patients in Shiraz, southern Iran.

Materials and Methods

This prospective DUR study was approved by the Ethics Committee of Shiraz University of Medical Sciences and was conducted in Ali-Asghar Hospital in Shiraz, southern Iran. An informed consent was obtained from each patient prior to the study. All inpatient cases of asthma or COPD who were started on intravenous (IV) loading dose of aminophylline in the emergency room (ER) were included in this study. Cases in whom aminophylline/theophylline were discontinued before steady state theophylline levels were reached, were excluded from the study. After 3 days at steady state condition, a trough blood sample was drawn from the patients. Plasma trough levels were determined by a turbidometer auto-analyzer (Cobas-Mira, Roche, Germany, detection limitation=0.1 mcg/ml).

Demographic characteristics of patients, along with clinical and paraclinical findings, and any ADE to aminophylline/theophylline that occurred during hospitalization were documented after a face-to-face interview with the patients and by using their files. All patients were followed until they were discharged from the hospital. DUR data were recorded in a questionnaire designed by a clinical pharmacist based on standard guidelines (Table 1)[7-11] for aminophylline/theophylline usage, administration, and monitoring. A log sheet consisting of 14 variables was prepared. A score of 1 or 0 was given to each variable depending on the fact that each variable was evaluated as appropriate or inappropriate, respectively. The appropriateness was defined based on the provided standard guideline (Table 1). A total score was given to each patient by adding the scores for each variable.

Statistical analysis (comparing serum concentration by t-test) was performed with the SPSS version 11.5 (SPSS INC, Chicago, IL, USA). p value <0.05 was considered significant.

Results

One hundred patients fulfilled the mentioned criteria and were enrolled into the study. Demographic characteristics and clinical information of our patients are shown in Table 2.

All patients who were admitted to the ER with acute asthma or COPD attacks not responding to standard treatment received a loading dose of aminophylline and referred to the ICU for further management of respiratory failure. All patients received a fixed dose regardless of their past history of theophylline use. Depending on the patients' signs and symptoms, 86% and 14% received maintenance dose of aminophylline and theophylline, respectively. All aminophylline doses were administered once daily as continuous infusion.

Dosage adjustment was not performed in any of the patients when substituting aminophylline with theophylline. Five percent of our patients received at least one drug that inhibited aminophylline/theophylline metabolism. Aminophylline/theophylline dose was adjusted empirically in all of these patients. Fifty three percent of the patients had at least one "other condition" that resulted in inhibition of theophylline metabolism. Dose adjustment was performed in 64.2 % (n=34) of these patients empirically.

Theophylline serum concentration range was 0-37 mcg/ml (7.94±5.4). A subtherapeutic trough level (<5 mcg/ml) was detected in 34%, while 4% had a level above the maximum therapeutic concentration (>20 mcg/ml). Ninety eight percent of the patients had at least one adverse event due to aminophylline/theophylline. Serious ADRs, defined according to the WHO definition, appeared in 8% of the cases. Although there was no statistically significant difference ($p\geq 0.05$) between serum concentrations of patients with and without nausea, mild tachycardia, abdominal pain, hypertension, and hyperglycemia, serum concentrations were significantly higher ($p<0.05$) in patients who developed vomiting, insomnia, nervousness, headache, and hypokalemia compared to patients in whom these symptoms did not appear.

A log sheet consisting of 14 items was completed for each patient. Eight variables (indication, monitoring parameters including: ABG, spirometry, LFT, signs and symptoms, and management of non-serious ADE, rate of infusion, and stability condition) were performed according to standard guideline, while loading and maintenance dose, changing aminophylline to theophylline, considering drugs and conditions which alter aminophylline dose requirement, measuring serum theophylline concentration, and management of serious ADRs were incongruent with the guidelines for all patients. Therefore the total score was equal for all patients in this study (8 out of 14).

Table1: Guidelines of aminophylline/theophylline usage

1 Indications:
Severe exacerbation of asthma that is refractory to inhaled short acting ß$_{2-}$ agonist and corticosteroids.
Severe exacerbation of COPD[a] that is refractory to other aggressive measures.
Loading dose (LD):
Patients not currently receiving theophylline preparations: 6 mg/kg.
Patients who are currently receiving theophylline preparations at least current 12 hours, serum theophylline concentration can be rapidly attained and LD is calculated according this formula:
LD= (Cp-Cp$_0$) x Vd x (weight)
Cp= desired serum theophylline concentration (mcg/ml)
Cp$_0$= the existing serum concentration if previously taking theophylline (mcg/ml)
Vd= volume of distribution
Weight= ideal or lean body weight. In obese patients (weight > 30% IBW) ideal body weight should be used. If this is not possible LD is 3 mg/ kg approximately.

2 Maintenance dose (MD):
Based on serum concentration and clearance of theophylline
MD= Cp$_{SS}$ x CL
Cp$_{ss}$= steady state serum concentration (mcg/ml)
CL= Clearance of theophylline (ml/min)
Transforming aminophylline to theophylline: dose of aminophylline x 0.8

3 Administration:
Dilute with IV fluid to a concentration of 1 mg/ml and infuse over 20- 30 min.
Maximum concentration= 25 mg/ ml
Maximum rate= 25 mg/ min

4 Drugs and conditions that alter the clearance of aminophylline/theophylline significantly (> 30%) in adult:
Induction: smoking, phenobarbital, phenytoin, rifampin
Inhibition: cimetidine, ciprofloxacin, enoxacin, pefloxacin, propranolol, OCP.
Hepatitis (Child-Pugh score>8), heart failure (NYHA[b] III, IV).

5 Monitoring:
Spirometry, evaluating sign and symptoms of asthma/ COPD[a] (dyspnea, coughing, wheezing, impairment of normal activity), ABG[c], serum concentration (5- 20 mcg/ ml)[d].

6 Adverse drug events:
10%:
Nausea, vomiting, headache, restlessness, nervousness, tachycardia
>1%:
Insomnia, irritability, rash, seizure, tremor.
Serious ADRs: seizure, cardiac arrhythmias
If a patient develops signs and symptoms of serious or persistent aminophylline/theophylline toxicity, a serum theophylline level should be measured and subsequent doses held.

7 Precautions:
Use with caution in patients with peptic ulcer, hyperthyroidism, seizure disorder, hypertension, and cardiac arrhythmias (excluding bradycardia).

8 Stability:
Aminophylline should not be used if discolored or if crystals are present.
Storage: room temperature
Appropriate solutions: dextrose water 5%, normal saline.

a- Chronic Obstructive Pulmonary Disease,
b- New York Heart Association,
c- Arterial Blood Gas,
d- Because of the wide interpatient variability of the metabolic clearance of theophylline, routine monitoring of serum theophylline level is important.

Table 2: Subject demographics, past medical history, duration of hospitalization, chief complains, social habits and diagnosis (N=100)

	No (%) or mean (± SD)
Sex	
Male	43 (43%)
Female	57 (57%)
Age (yrs)	65.6 (±14.7)
Ideal body weight (kg)	60.4 (±11.0)
Diagnosis	
COPD[a]	54 (54%)
Asthma	46 (46%)
Duration of hospitalization (days)	4.8 (±1.8)
Past medical history	
Obesity[b]	33 (33%)
Hypertension	40 (40%)
Ischemic heart disease	21 (21%)
Heart failure	12 (12%)
NYHA[c] I	2(2%)
NYHA[c] II	6 (6%)
NYHA[c] III	2 (2%)
NYHA[c] IV	2 (2%)
Hyperlipidemia	12 (12%)
Seizure	4 (4%)
Diabetes mellitus	2 (2%)
Social habits	
Cigarette	25 (25%)
Opium	10 (10%)
Water pipe	4 (4%)
Chief Complains	
Dyspnea	60 (60%)
Cough	60 (60%)
Fever	28 (28%)

Chronic Obstructive Pulmonary Disease, a- >30% above ideal body weight, c- New York Heart Association

Discussion

Aminiophylline is occasionally used in patients with severe exacerbations of asthma or COPD that are refractory to high dose short-acting $ß_2$ agonist and systemic corticosteroids. The role of aminophylline for managing asthma exacerbations is controversial.[12-16] According to our guideline, the indication for aminophylline administration was appropriate in 100% of the patients.

In a retrospective study performed in Taiwan it was shown that physicians from district hospitals prescribed parenteral amoniphylline as first line and most emergency physicians did not adhere to acute asthmatic exacerbation management guidelines.[17]

Theophylline has a narrow therapeutic index and a wide variation in hepatic metabolism and clearance. Individualizing theophylline's drug dosage and dosing interval according to serum level can minimize toxicity and maximize the therapeutic benefit of the drug. Therapeutic serum concentration of theophylline has a range between 5-20 mcg/ml.[18] Theophylline has anti-inflammatory and bronchodilatory effects. Anti-inflamatory effects of theophylline can be seen at concentrations lower than 10 mcg /ml while its bronchodilatory effect is seen with levels of 10-20 mcg/ml.[19] In this study, serum theophylline trough levels were measured in order to determine if patients were receiving adequate doses of the drugs. The physician performed the dosage adjustment in a blinded fashion. Most of our patients had a trough plasma level within the therapeutic range (62%). According to the protocol, determining the loading and maintenance dose requires a plasma level. On the other hand, some patients had a condition (acute heart failure, hypoxia, drug use with inhibitory effect on theophylline metabolism, smoking

cessation)[7,20] that required dose adjustment according to the drug level. Therefore, although most of our patients had a plasma level within therapeutic range, this was somehow coincidental and dosing of aminophylline/theophylline in our patients was not performed according to the guideline.

In a retrospective cohort study that was performed in United States, serum theophylline monitoring was not conducted in 59% of the patients.[21] In another study, 80% of patients had a sub-therapeutic theophylline concentration, while only 20% had a concentration within the therapeutic range (10-20 mcg/ml).[22] In our patients Aminophylline/theophylline dose adjustment was performed based on the monitoring parameters. This approach was consistent with guidelines, although dosage adjustment was performed regardless of serum concentration.

With a serum concentration above 20 mcg/ml, the rate of ADEs increased but there are many controversies regarding the relationship between theophylline serum concentration and the occurrence of ADEs.[23,24] Ohta *et al*. showed that very few ADRs were caused by aminophylline (2 cases/692 patients), and no serious ADRs were reported. They concluded that aminophylline is a highly safe drug when used appropriately.[25] One reason for the difference between the ADE reports in other studies and this study was the fact that we have reported all ADEs in an active way, while other studies mentioned only reported ADRs and the reporting was spontaneous. It is of note that our patients received many drugs concomitantly with theophylline, leading to potentiation of many of theophylline's ADRs (e.g.: tachycardia, hypertension, Gastrointestinal upset).

Due to the fact that serum levels of aminophylline/theophylline is not monitored in this hospital, and 6 out of 14 variables that were evaluated in this study required a serum concentration monitoring in order to be considered 'appropriate', all patients received a total score of 8/14 for their aminophylline/theophylline utilization evaluation. In fact all other variables that did not require a serum level were appropriate in all patients according to the guideline. This means that establishing a therapeutic drug monitoring (TDM) for this drug can pull up the DUR score from 8 to 14, and probably there is no lack of knowledge but a lack of equipment.

According to the results of this study, the most considerable problem in aminophylline/theophylline usage in our hospital was the ignorance of the important role of pharmacokinetics in optimizing aminophylline/theophylline use. Training healthcare providers, continuous education, direct supervision of Pharmacy and Therapeutic Committee on utilization of aminophylline/theophylline and it's TDM, providing equipment and trained personnel for TDM, and presence of a clinical pharmacist is recommended. Performing a population pharmacokinetic study will also be a good guidance for improving the aminophylline/ theophylline usage in our population.

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Conflict of interest: None declared.

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