

## Theophylline blood levels in Sri Lankan asthmatics: comparison of two methods of assay

A K E Goonetilleke<sup>1</sup>, T M J Munasinghe<sup>2</sup>, H C Cooray<sup>3</sup>, W K Balasuriya<sup>4</sup> and N Fernando<sup>5</sup>

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### Abstract

**Objectives** To assay theophylline blood levels in a sample of Sri Lankan chronic asthmatics taking oral theophylline, and to evaluate a simple and cost effective ultraviolet spectrophotometric assay for theophylline levels in blood.

**Setting** Chronic asthmatics taking oral theophylline attending medical clinics at the National Hospital of Sri Lanka (NHSL) were recruited for the study. Blood samples were collected from recruited patients on their subsequent clinic visit.

**Design and methods** A cross-sectional study of theophylline blood levels. Blood samples were assayed for trough theophylline levels using two methods: an automated homogeneous enzyme immunoassay (EMIT), and a low cost ultraviolet spectrophotometric method.

**Results** Only 2 patients of the 24 had theophylline blood levels in the accepted therapeutic range (10 to 20 µg/ml) (3,4); 19 patients had levels under 5 µg/ml. A correlation coefficient of 0.99 was obtained in the statistical comparison of the two methods, indicating that the spectrophotometric method has similar accuracy as the reference EMIT assay.

**Conclusions** The results signal a need for monitoring of theophylline in asthmatics when accepted clinical indications are present. The ultraviolet spectrophotometric method is ideal to initiate therapeutic drug monitoring (TDM) in the country because of its low cost (about Rs. 55 per assay), requiring only a UV recording spectrophotometer.

### Introduction

Asthma is common in Sri Lanka. It caused 878.8 hospitalisations and 5.1 deaths per 100 000 population in 1999 (1). Theophylline is a widely used bronchodilator agent (2) in prophylaxis and treatment of acute attacks of asthma. It has a narrow therapeutic index, with a therapeutic range of 10 to 20 µg/ml (55 to 110 µmol/l). Signs of toxicity appear when blood levels are above this range, and the drug is therapeutically ineffective when levels are below this (3,4). Maintaining blood levels within this narrow range is made difficult because theophylline levels are affected by the patient's age and health, life style factors such as smoking and alcohol intake, intercurrent illness, variation in pharmaceutical formulation of the drug,

and concomitant use of medications that influence the activity of the hepatic cytochrome P450 enzyme system. As a result patients on fixed dosage regimes may have widely varying blood levels indicating a need to individualise dose in such patients.

### Methods

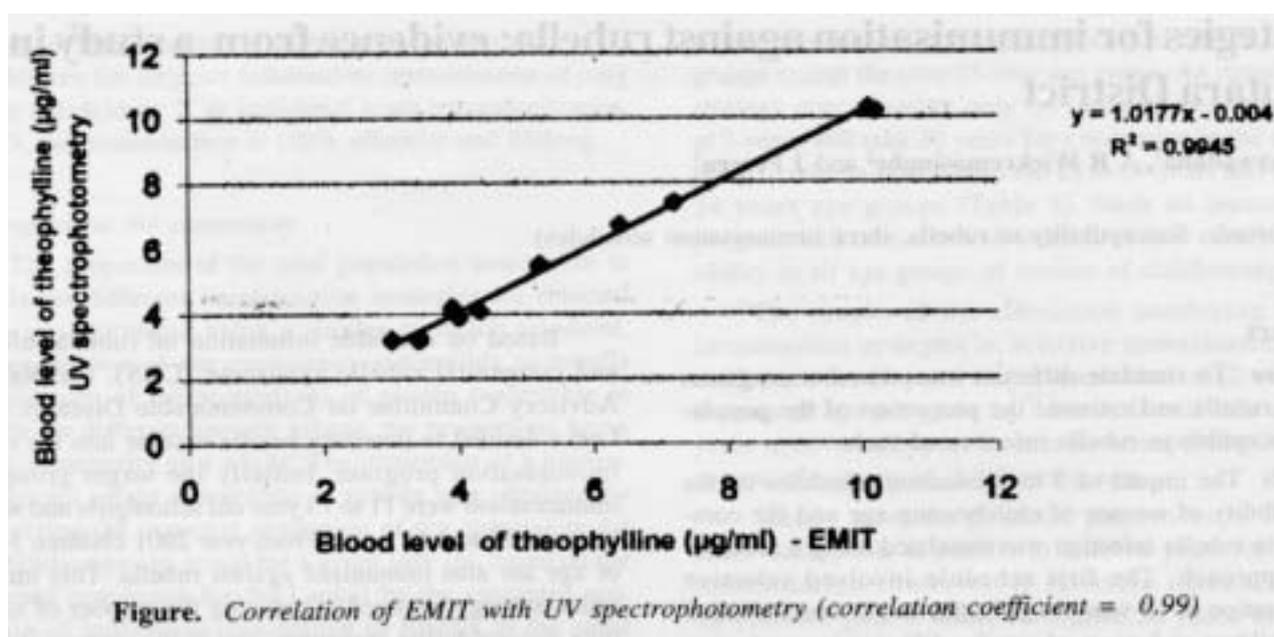
24 patients (10 males) suffering from chronic asthma on oral theophylline for over 3 months and attending regular medical clinics at the NHSL were recruited for the study over a period of four weeks. Written informed consent was obtained from all patients. Ethical approval was obtained from the research committee of the Medical Research Institute.

The average age was 55 years (range 42 to 72) and the weight 55.4 kg (range 43 to 72). Coexistent diseases included essential hypertension, diabetes, ischaemic heart disease, emphysema and chronic bronchitis. Concurrent medication included salbutamol, beclomethasone (inhaled), prednisolone, nifedipine, verapamil, diltiazem, prazosin, captopril, aspirin, metformin, glibenclamide, folic acid and paracetamol. None of these drugs are known to significantly affect theophylline clearance. The xanthine preparations dispensed to the patients were theophylline 125 mg and choline theophyllinate/oxtriphylline 100 mg, both of which have identical bioavailability (2). The subjects were asked to omit their morning dose of theophylline on the day of blood collection so that the trough level of the drug could be assayed. Apart from being requested to refrain from taking tea or coffee on the morning of blood collection, there were no other dietary restrictions.

A single blood sample of 10 ml was drawn from an arm into a disposable syringe. Samples were immediately transferred to plastic tubes each containing 200 units of heparin, sealed, labelled, and taken to the Medical Research Institute. Here the samples were centrifuged at 3000 rpm for 10 minutes and the plasma was stored at -70° C in a ultrafreezer until analysis. The name, address, age, weight, disease history, concurrent medication, and dietetic history including tea and coffee intake of each patient were recorded.

Each blood sample was assayed for theophylline using two methods: ultraviolet spectrophotometric method (5) and EMIT 2000 homogeneous enzyme immunoassay for theophyllin (6).

<sup>1</sup>Senior lecturer, <sup>3</sup>Student (BSc Pharmacology), <sup>4</sup>Lecturer, Department of Pharmacology, University of Sri Jayawardenapura, Nugegoda; <sup>2</sup>Pharmacologist, Medical Research Institute, Colombo 8. (Correspondence: AKEG, tel: 01 595742; email: akeg@sltnet.lk. Submitted 26 August 2001, revised version accepted 15 March 2002).



## Results

Both methods showed that only 2 patients had theophylline levels within the therapeutic range; 92% of the sample population was sub-therapeutic (less than 10 µg/ml) and 19 patients ie. 79% of the sample population, had blood levels under 5 µg/ml. A statistical comparison was carried out between the results obtained using the values of the 12 samples, which gave an acceptable result from both methods (ie. clear peak in the UV spectrophotometric method and a blood level over 2.5 µg/ml in the EMIT). The values obtained by the two methods had a correlation coefficient of 0.994, indicating a very close correlation between the two methods (Figure).

## Discussion

This study showed that the sample of asthmatic patients surveyed had grossly sub-therapeutic theophylline blood levels. The results signal a need to use therapeutic drug monitoring as a guide to monitor patient compliance and individualise dosage during theophylline therapy. The UV spectroscopic method appears to be well suited for this purpose. The results of this method correlated well with results obtained from the automated system, and it can be implemented with little extra outlay as most laboratories have a UV spectrophotometer and trained technicians have a sound knowledge of UV spectrophotometry. The method has a clear advantage over the automated analyser method in terms of capital and recurrent costs. The cost for an assay was about Rs. 55. With minor modifications, this method can also be used for phenobarbital, phenytoin, procainamide and quinidine (5). The method has some disadvantages; it is labour intensive,

requires 3 ml of plasma or serum, has a long assay time (about 2 h), and the number of samples that can be done simultaneously by an operator is limited to about 10.

Poor compliance owing to standard release formulation products (theophylline or choline theophyllinate), necessitating thrice-a-day dosing, may have been a reason for the sub-therapeutic drug levels detected in the majority of patients. In many countries, immediate release theophylline formulations are being replaced with sustained release formulations (7). This will improve patient compliance and give blood levels closer to the accepted therapeutic range. We strongly recommend that this trend be followed in Sri Lanka, too.

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