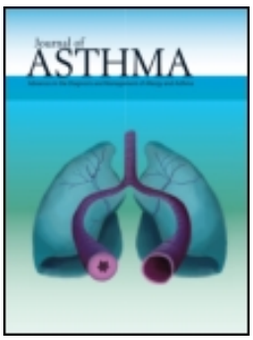

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CLINICAL ACUMEN

Brief Report: Poor Bioavailability of Sustained-Release Theophylline. A Case for Liquid Theophylline

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INTRODUCTION

Effective management of asthmatic patients using theophylline therapy requires careful monitoring of serum theophylline concentration (STC) (1). Frequently, concentrations are noted to be subtherapeutic and poor patient compliance is usually held responsible. We present here a case of a young adult who was unable to achieve theophylline concentrations in the therapeutic range while taking various sustained-release theophylline (SRT) preparations in high doses. After pharmacokinetic analysis, we discovered that she malabsorbed SRT preparations, but demonstrated normal absorption of a liquid, rapidly absorbed formulation.

CASE HISTORY

JH is a 20-year-old white female referred to the National Jewish Center for Immunology and Respiratory Medicine for progressively worsening asthma. She presented a history of lifelong, perennial asthma with daily exacerbations and nocturnal awakening despite taking Theo-Dur 300 mg tid (18 mg/kg/day), inhaled albuterol 2 puffs 6-8 times/day, and inhaled beclomethasone 2 puffs qid. Spontaneous wheezing often occurred 3-4 hours after using albuterol. She also received several short courses of prednisone each year for asthma exacerbations of unclear etiology. She reported poor responses to various SRT preparations despite doses up

to 1000 mg/day (20 mg/kg/day). All prior theophylline concentrations drawn while our patient was taking Slo-bid Gyrocaps, Theo-Dur tablets, or Theolair-SR tablets were less than 6 μg/mL. She reported no history suggestive of malabsorption. Additionally, she denied smoking, medication use other than those mentioned above, or any recent changes in diet.

Her examinaton revealed a well-nourished, well-developed young woman with bilateral diffuse expiratory wheezing. Spirometry demonstrated moderate airway obstruction reversible to >90% of predicted with inhaled bronchodilator. An STC drawn 5 hours after her morning dose was 1.3 μg/mL. We then hospitalized our patient in order to study her theophylline kinetics.

METHODS AND RESULTS

A theophylline kinetics study was performed as follows: a heparin lock was placed in the arm and flushed periodically with heparin and saline. The patient received her usual dose of Theo-Dur 300 mg every 8 hours. Medical personnel carefully ensured that each dose was ingested. Two ml of blood was withdrawn for measurement of STC every 2 hours for 24 hours. The results are shown in Figure 1.

The average STC and standard deviation was 3.9 ± 0.81 μg/mL (range 1.8 to 5.6 μg/mL). Her theophylline clearance, calculated using the following equation:

$$Cl_{oral} = \frac{Cl}{F} = \frac{D}{AUC} = \frac{D}{Cp_{ss\tau}}$$

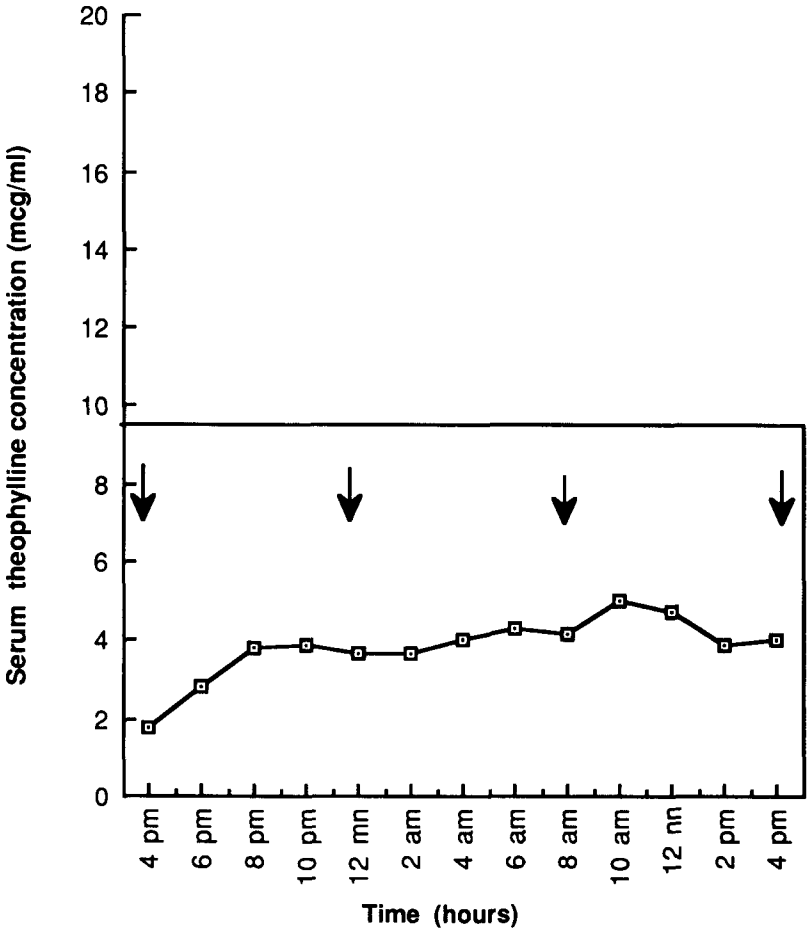

Figure 1. Serum theophylline concentrations (STC) obtained during 24-h pharmacokinetics study. Arrows indicate oral theophylline doses (300 mg). Horizontal line indicates lower limit of therapeutic STC.

was 188 mL/h/kg (normal adult value 50 ± 25 mL/h/kg), where F = oral bioavailability factor, D = dose, AUC = area under the curve, Cp_{ss} = average steady-state concentration, and τ = dosage interval. This high value indicates either rapid theophylline metabolism or poor absorption. Since she was taking no medications known to induce theophylline elimination (see Discussion), we concluded that poor absorption was the cause of her low STC.

JH was then given Somophyllin liquid 150 mg (3 mg/kg), which has excellent oral bioavailability. Since the volume of distribution of theophylline averages 0.5 L/kg, this dose was expected to produce an increase in STC of approximately 6 mg/L (or 6 μg/mL). Her predose theophylline level was 2.7 μg/mL at 10 a.m.; this increased to 8.8 μg/mL three hours following a single oral dose. She complained of shakiness at that time, the first occasion that she had ever experienced theophylline effects.

She was discharged on Somophyllin liquid 150 mg every 6 hours (12 mg/kg/day). One month later her physician increased her dose to 200 mg every 6 h; an STC (2 h after her first daily dose) was 12 μg/mL.

Three months after her evaluation, she reported fewer episodes of unprovoked wheezing and had not required prednisone since starting Somophyllin.

DISCUSSION

Multiple studies have demonstrated the efficacy of theophylline therapy in chronic asthma, used both alone (3) or in combination with beta-adrenergic agonists (4). Theophylline administration has also been noted to decrease the requirement for supplemental oral corticosteroids (5). For these reasons we felt JH would particularly benefit from optimized theophylline therapy. An important obstacle in realizing this goal was a history of subtherapeutic STCs despite high doses of a variety of SRT preparations.

In considering the causes of a low STC, several factors must be considered:

1. Timing of blood sampling. When using a rapidly absorbed or SRT preparation, blood should be drawn 1–2 or 4–6 h postdose, respectively, to most closely approximate the maximum STC.
2. Compliance. Good compliance with therapy can be ensured only by administering the drug in an observed setting.
3. Rapid drug elimination. Young age, medications (including anticonvulsants, rifampin, and oral beta-agonists) cigarette smoking, and diet (charcoal-broiled foods and changing from low protein-high carbohydrate to high protein-low carbohydrate) can result in increased drug elimination (1,6,7).
4. Decreased drug absorption. Several factors can affect both the rate and extent of theophylline absorption. The rate of absorption of some SRT preparations, as well as liquids and plain tablets, may be reduced by food and supine posture (8,9). In children, circadian variation in STC formulations has been noted frequently with several SRT formulations (10,11). More recently, an adult patient studied at our own institution demonstrated markedly reduced absorption of both sustained-release and plain tablet preparations (12). Additionally, any illness that results in intestinal malabsorption can theoretically reduce theophylline absorption.

The patient described here is the first, to our knowledge, with a selectively impaired ability to absorb sustained-release theophylline throughout the entire day. She was, however, able to absorb a liquid preparation normally. Although we were unable to explain the basis for this selective drug malabsorption, her case demonstrates the value of using rapidly absorbed theophylline formulations under special circumstances. Additionally, it illustrates the value of a pharmacokinetic evaluation in a patient who requires theophylline for control of their asthma, but is noted to have subtherapeutic STCs on multiple assays.

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