Theophylline Dosing and Theophylline Level Testing in a Family Practice Population

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Theophylline level testing enables the physician to monitor patients on theophylline and maintain benefit vs risk at an optimum ratio. This study consisted of a retrospective chart review of 53 patients who had a total of 103 serum theophylline level determinations (STLDs) over a 12-month period. The study was designed to look at reasons why physicians ordered STLDs and to what extent those results influenced subsequent theophylline prescribing. Findings showed that a large number of STLDs were ordered on asymptomatic patients with no recent dose change or initiation of therapy and no recent hospitalization or emergency room visit. The most common reason for ordering an STLD was presentation with symptoms or signs of asthma and no other recent events. On several occasions when low results were obtained, theophylline dosage was not increased. In some of these cases the patient's clinical presentation may have influenced the decision to maintain the same dosage. Use of erythromycin and smoking status were observed to affect theophylline clearance. Most physicians failed to document time of last theophylline dose, which hindered accurate interpretation of STLDs.

Theophylline is a widely used drug that has been available since the 1920s. It has been used to treat Cheyne-Stokes respirations and apnea and bradycardia of the newborn, and as an adjunct in the treatment of acute pulmonary edema. Its most common usage, however, has been as a bronchodilator in the acute and chronic treatment of asthma. Theophylline has come to be associated with several serious side effects. Both benefit and incidence of side effects have been shown to be directly related with serum concentration of the drug. It is generally accepted that the therapeutic serum concentration range of theophylline is 55 to 110 μmol/L (10 to 20 mg/L). Serum concentrations between 110 and 165 μmol/L (20 and 30 mg/L) often produce nausea, vomiting, diarrhea, headache, insomnia, and irritability. Higher concentrations may produce seizures, brain damage, arrhythmias, and death.

The February 1987 issue of *American Druggist* tabulated the 200 most prescribed drugs in the United States for 1986. One of the numerous available theophylline preparations (Theodur) ranked number 17 on that list. Several articles have studied the use of theophylline level testing in hospital patients,[1–5] but relatively little has been written concerning theophylline level testing in ambulatory patients.[6–8] With a drug this widely used and one that is potentially toxic, it was felt that it would be useful to investigate prescribing and monitoring patterns in a family practice population.

There were several goals and objectives of this study. One was to ascertain the reasons and frequency with which serum theophylline level determinations (STLDs) were ordered. Another goal was to determine how much test results influenced subsequent theophylline prescribing. Although test results are very important, especially when they reveal a potentially life-threatening situation, it was hoped that physicians would be shown to not necessarily "treat a number" but look instead at the clinical presentation and individualize care.

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METHODS

This study consisted of a retrospective chart review involving 53 patients (age range 5 to 83 years) who had a

total of 103 STLDs over a 12-month period from March 21, 1985, to March 20, 1986. All theophylline assays were done on the same machine, a Seralizer reflectance photometer, manufactured by the Ames Division of Miles Laboratories. All assays were done at the Family Practice Center of the Medical College of Georgia.

A standardized database was completed for each STLD reviewed. This database included such demographic data as name of patient, age, race, sex, and weight. The test date, physician prescribing and physician ordering the STLD, theophylline dose, and date when the current dose was first prescribed were also recorded. Another section included current medications and possible interfering factors that existed with the patient. The last section of the database involved reasons why the STLD was ordered, whether there was documentation of when the last dose was given, the test result, and what kind of follow-up was given after the result was obtained.

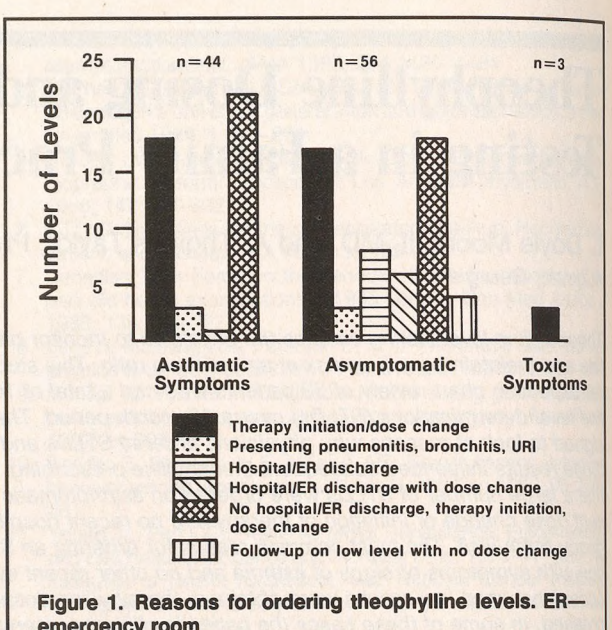

Figure 1. Reasons for ordering theophylline levels. ER—emergency room

RESULTS

Several different reasons were noted regarding why STLDs were ordered (Figure 1). Patients could be broadly divided into three groups: those with asthmatic symptoms, such as shortness of breath and wheezing or evidence of wheezing on physical examination; those patients with toxic symptoms such as nausea, vomiting, irritability; and those patients who were free of asthmatic or toxic symptoms. These groups could be further subdivided: (1) some patients had either been started on theophylline or had had a dose change in the past month; (2) a small group presented with either pneumonitis, bronchitis, or upper respiratory tract infection; (3) several patients had been discharged from the hospital or emergency room for respiratory-related illness within the past month with no dose change; (4) some had been discharged from the hospital or emergency room and had had a theophylline dose change at the time of discharge; (5) a large group of patients (represented by the cross-hatched lines in Figure 1) had had no initiation of therapy, no dose change, theophylline level determination, or discharge from hospital or emergency room in the past month; and (6) a group similar to group 5 had the distinguishing characteristic of having had subtherapeutic STLDs obtained during the past month and were getting a follow-up level determined.

There were more STLDs listed under the asymptomatic group; however, the largest single subgroup represented patients who presented with signs or symptoms of asthma and no other recent events (Figure 1). Many patients, however, fit into the category of recent dose change or initiation of therapy. Also, a relatively large number of patients had STLDs ordered for apparently routine purposes, ie, asymptomatic patients with no recent dose change or initiation of therapy, or no recent discharge from hospital or emergency room.

Figure 2 depicts theophylline prescribing after theophylline level results were obtained. Results are divided into low, therapeutic, and high categories, defined as less than 55 μmol/L, 55 to 110 μmol/L, and greater than 110 μmol/L (10 mg/L, 10 to 20 mg/L, and greater than 20 mg/L), respectively. It was noted that on 28 occasions when a low level was found, the patient was continued on this same dose, and on three occasions when high levels were determined, there was no documented decrease in dosage. These cases were further evaluated.

Theophylline levels less than 55 μmol/L (10 mg/L) were subdivided into those 27.5 to 55 μmol/L (5 to 10 mg/L) and those less than 27.5 μmol/L (5 mg/L). Of the low levels associated with no dose change, the actual value was 27.5 to 55 μmol/L (5 to 10 mg/L) for 17 of 28 cases, with 13 of those 17 cases being asymptomatic and 4 being symptomatic. There were five cases with levels lower than 27.5 μmol/L (5 mg/L) who were asymptomatic, and in only six cases was the level lower than 27.5 μmol/L (5 mg/L) and the patient had signs or symptoms of asthma.

On closer examination of the three cases with high levels and no documentation of dose change, some additional information was obtained. In the first case, a 71-year-old man with a level of 116.6 μmol/L (21.2 mg/L), the patient had previously been found to require maintenance levels in a range of 93.5 to 121 μmol/L (17 to 22 mg/L) for

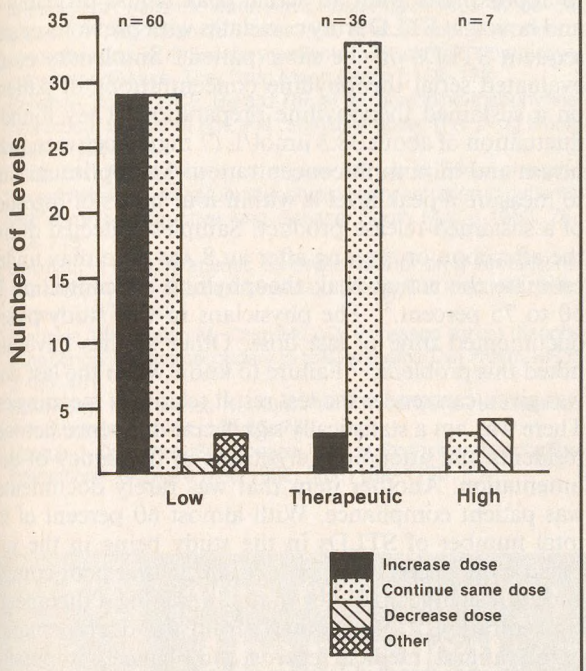

Figure 2. Theophylline prescribing after theophylline results obtained

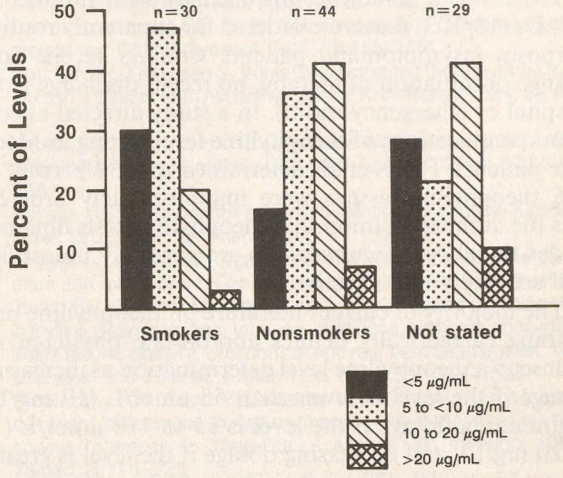

Figure 3. Distribution of theophylline levels with regard to smoking status

optimal benefit. The second case was a 34-year-old woman with a level of 132.6 μmol/L (24.1 mg/L) in the midst of an exacerbation of asthma. She was admitted to the hospital within a few days, and her theophylline level was closely monitored. In the last case, a 53-year-old man with a level greater than 165 μmol/L (30 mg/L), the patient was indeed notified, instructed to hold doses, and return the next day for follow-up.

For three of the 103 STLDs studied, patients were taking or had recently finished courses of erythromycin. Two of these patients had STLDs prior to erythromycin use for comparison. The first patient had a previous level of 27 μmol/L (4.9 mg/L). Her theophylline dose was subsequently increased by 50 percent. A repeat test on this new dose with the concomitant use of erythromycin yielded a value of 67.7 μmol/L (12.3 mg/L), an overall increase of 150 percent. The second patient had two low serum concentrations previously, but on the same dose, when taking erythromycin, a therapeutic serum concentration was obtained. The third patient was taking a moderate dose of theophylline, 300 mg every 12 hours, or 12.1 mg/kg/d, but her STLD was 125.9 μmol/L (22.9 mg/L).

The distribution of theophylline levels with regard to smoking status was also evaluated (Figure 3). When comparing smokers with nonsmokers, refer to the third column for each group. Only 20 percent of smokers' STLDs were in the therapeutic range, whereas nonsmokers' STLDs were in the therapeutic range 41 percent of the time. Combining columns one and two, smokers had STLDs below 55 μmol/L (10 mg/L) 77 percent of the time, whereas nonsmokers had low STLDs 52 percent of the time.

In this study, the time of the last theophylline dose was documented in the medical chart for only 13 of 103 STLDs reviewed. Attending physicians as a group documented time of last dose for 4 of 39 STLDs, whereas resident physicians documented time of last dose for 9 of 64 STLDs. Of the 30 physicians who ordered STLDs, 22 of them never documented the time of last dose.

DISCUSSION

It is difficult to assess why any specific serum theophylline level determination was ordered. It appears that presentation with signs or symptoms of asthma is the most common initiating factor. This finding was also noted in Culbertson and Osborn's study.[7] The study of Bredon et al[8] noted that 65 percent of the medical records they reviewed indicated no reason why the theophylline assay was ordered. In Figure 1 patients are divided into several distinct categories, but it is not entirely clear whether a patient's particular category was the actual reason why his or her theophylline test was ordered.

There was a somewhat disturbingly high number of STLDs (18/103) that were ordered for apparently routine purposes (asymptomatic patients with no recent dose change or initiation of therapy, no recent discharge from hospital or emergency room). In a study directed at economic implications of theophylline level testing in Medicare patients, Farris et al[3] determined that 30 percent of 146 theophylline assays were inappropriately ordered. It is the authors' opinion that theophylline tests obtained under the above circumstances are generally unjustified and are rarely cost effective.

The majority of current literature on theophylline prescribing categorically defines appropriate physician response to a theophylline level determination as increasing dosage if the level is lower than 55 μmol/L (10 mg/L), maintaining dosage if the level is 55 to 110 μmol/L (10 to 20 mg/L), and decreasing dosage if the level is greater than 110 μmol/L (20 mg/L). These rigid guidelines may hinder the clinician's individualization of patient care. Some clinicians extend the therapeutic range of theophylline concentrations to include all values from 27.5 to 110 μmol/L (5 to 20 mg/L). Indeed, some patients with bronchospasm do obtain satisfactory relief with maintenance levels of only 27.5 to 55 μmol/L (5 to 10 mg/L). In this study there were 13 cases in which an asymptomatic patient had a theophylline concentration of 27.5 to 55 μmol/L (5 to 10 mg/L). A good argument can be made that the prescribing physician acted appropriately in not increasing theophylline dosage.

A number of different drugs, disease states, and other factors have been shown to affect the clearance of theophylline. Cimetidine, erythromycin, oral contraceptives, caffeine, isoproterenol, and verapamil have all been shown to decrease the clearance of theophylline.[9–13] Phenytoin, barbiturates, and rifampin have been demonstrated to increase the clearance of the drug.[11,14] Theophylline clearance is variably and sometimes markedly impaired with heart failure and liver failure.[15] It is also reduced by some viral infections and during the third trimester of pregnancy.[15,16] In hyperthyroidism and cystic fibrosis theophylline clearance tends to be increased.[15,17] Administration of influenza vaccine has been shown to significantly decrease elimination of theophylline.[18,19] Theophylline clearance tends to decrease with age from childhood to old age. Cigarette smoking and the use of marijuana enhance the clearance of theophylline.[20,21] This study demonstrated trends that support previous findings that erythromycin decreased and cigarette smoking increased theophylline clearance.

To assess the true significance of a given STLD, it is important to know whether the value represents a peak level or a trough level or somewhere in between. Documentation of when the last dose of theophylline was given allows the physician and others reviewing the chart later to approximate what an actual peak would probably be and how that STLD truly correlates with previous or subsequent STLDs on the same patient. Smolensky et al[22] evaluated serial theophylline concentrations in patients on a sustained theophylline preparation. They found a fluctuation of about 38.5 μmol/L (7 mg/L) between maximum and minimum concentration. The optimum time to measure a peak level is within four hours of ingestion of a sustained-release product. Samples collected during the afternoon or evening after an 8 AM dose may underestimate the actual peak theophylline concentration by 50 to 75 percent.[22] The physicians in this study poorly documented time of last dose. Other studies have also noted this problem.[2,8] Failure to know when the last dose was given can render the test result relatively meaningless. There was not a statistically significant difference between residents and attending physicians in frequency of documentation. Another item that was rarely documented was patient compliance. With almost 60 percent of the total number of STLDs in the study being in the subtherapeutic range, it is highly probable that poor compliance is a significant factor in not obtaining a therapeutic concentration. Unfortunately, from the documentation in the patients' medical records, compliance is impossible to determine.

In conclusion, serum theophylline level testing is a valuable tool to monitor the benefits and risks of this useful but potentially toxic agent. The physicians in this study did reasonably well prescribing theophylline, ordering STLDs, and utilizing that information to optimize the patient's care. Physicians need to document time of last dose when ordering drug level determinations, be aware of factors that can influence a drug's clearance, and always individualize medical care with regard to each patient's specific clinical presentation.

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