Unraveling The Mysteries Of Serum Theophylline Levels: A Patient Care Report In The Light Of Pharmacokinetics

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Abstract: One of our patients had trouble maintaining therapeutic and safe levels of theophylline, even though we were careful in planning and monitoring her drug regimen. This case report shows how we were able to use principles of pharmacokinetics to distinguish among plausible explanations for her experience. We discovered that she was not taking the drug consistently as prescribed and that supervised administration resolved apparent contradictions between doses and serum levels. We believe that physicians can use the same information and methods that we used to get better and safer results from theophylline therapy. (JABFP 1988; 1:282-7.)

Deriving as much information as possible from laboratory tests is in the best interest of the patient and is a reasonable goal of cost-effective medical practice. Unfortunately, however, serum drug concentration determinations frequently are used in an inefficient fashion.[1] Although most clinicians realize the importance of allowing the patient's serum drug concentration to reach a steady-state value before performing such tests, and some are careful to time the sample collection appropriately in order to measure a peak or trough concentration, few routinely go so far as to calculate the pharmacokinetic characteristics of an individual patient. While estimating the patient's volume of distribution, elimination rate constant, and serum half-life for a particular drug is not necessary in many instances, these calculations (which can be made with relative ease if samples are collected appropriately) can be very useful, especially when a drug has a narrow therapeutic range and wide interpatient variability in the dose-to-serum concentrations. Theophylline is such a drug. It has a narrow therapeutic serum concentration range of 10–20 μg/mL. Wide interpatient variability in pharmacokinetic values requires individualized dosing regimens and may produce considerable fluctuations between peak and trough serum concentrations in patients with rapid elimination rates.[2-4] Sustained release theophylline preparations have been developed in an attempt to minimize serum concentration fluctuations, but significant variability in absorption has been reported.[5-8]

Theophylline serum assays are useful in assessing therapeutic efficacy and in preventing or confirming toxicity, especially if the sample is collected at a specific time in the dosing interval. The following case report describes how assay results were used to estimate a patient's unusual pharmacokinetic values, which, in turn, were employed to tailor a dosing regimen, and to investigate a potential dilemma of sporadic absorption versus intentional noncompliance.

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Patient Care Report

The patient was a 35-year-old nonsmoking white woman who was 165 cm tall and weighed 95 kg (ideal body weight, 56.5 kg). Her only chronic medical problem was asthma since childhood, and it was well controlled with oral theophylline and inhaled beclomethasone until approximately 4 months before the most recent hospital admission, when she began to experience recurrent, acute exacerbations. During this period, she was hospitalized twice and treated with a continuous infusion of aminophylline at a rate of 26.4 mg/kg/day of theophylline (based on her

ideal body weight of 56.5 kg), which produced serum theophylline concentrations of 21 μg/mL and 19.5 μg/mL, respectively. Oral dosing, however, proved much more difficult. Regimens that employed five different products and ranged from 200 mg every 6 hours to 600 mg every 6 hours apparently produced serum theophylline concentrations from 2 μg/mL to 21 μg/mL. Such fluctuations occurred during hospitalizations and following discharge. A therapeutic level with orally administered theophylline was achieved only with Slo-Phylline™ tablets, a rapid release theophylline product, but the patient experienced nausea and diarrhea while on this agent, possibly due to rapid attainment of peak blood concentrations.

At the time of the most recent hospitalization, the patient experienced headache, blurred vision, nausea, and tremulousness, and her theophylline serum concentration was 41 μg/mL while receiving oral aminophylline 600 mg every 6 hours. Aminophylline was discontinued, and theophylline levels drawn 5 and 11 hours later were 32 μg/mL and 22 μg/mL, respectively. She was transferred to another hospital for pharmacokinetic assessment of her theophylline dosing problem. After her theophylline serum concentration decreased, a continuous aminophylline infusion was started, which provided 22.1 mg/kg/day (0.92 mg/kg/hr) of theophylline (based on ideal body weight). This dosage produced an average steady-state concentration of 14.8 μg/mL based on four levels of 14.6, 14.6, 15.6, and 14.5 μg/mL each drawn 12 hours apart on 2 consecutive days. She was then changed to oral aminophylline, 400 mg every 6 hours (22 mg/kg/day theophylline), but serial peak and trough theophylline concentrations during the first 2 days of this regimen were all less than 2 μg/mL, and the dose was increased to 600 mg every 6 hours. Although the nurse's medication record indicated that all doses had been given, the patient was confronted about the possibility of noncompliance, which she convincingly denied. Early the following morning, however, she awoke with complaints of chest pain, headache, restlessness, and nausea. She suggested that the nurse check her theophylline concentration, and her stat level was 33.4 μg/mL. The drug then was withheld for 17 hours, and she was changed to aminophylline liquid (21 mg/kg/day), which was administered in divided doses in the presence of the nurse and followed by a glass of water. Her serum theophylline concentration on this dosage regimen reached peak levels of 17 to 24 μg/mL and trough levels of 13.6 to 17 μg/mL. She was discharged on a theophylline dosage of 16 mg/kg/day.

Pharmacokinetic Principles

The management of this patient raises several issues that may be encountered with theophylline therapy. Published theophylline dosing guidelines are based on average population pharmacokinetic values.[2,9] Studies have shown large inter- and intra-patient variability in absorption, distribution, and elimination of theophylline, necessitating individualized dosage regimens.[6,8] Before examining how this patient's regimen was individualized, however, it may be worthwhile to review some of the relevant pharmacokinetic concepts and related equations (see Appendix).

Linear Kinetics

It should be noted that the principles discussed here apply only to drugs with linear kinetics. That is, with chronic dosing, a given increase in dose will produce a proportional increase in serum concentration, and the greater the serum concentration, the more drug will be eliminated from the serum over a given period of time. Some drugs, such as phenytoin and other anticonvulsants, exhibit nonlinear or partially saturable kinetics. With such agents, increasing the dose as the metabolic pathways become saturated will lead to a much greater than proportional increase in the serum concentration because the elimination of the drug cannot be increased proportionately. Although the kinetics of theophylline metabolism may become slightly nonlinear or saturated in some patients at high serum concentrations, this is not the usual case and, therefore, the principles of linear kinetics can be applied to almost all patients taking theophylline.

The rate of rise and the degree of change in the serum concentration following a dose of theophylline are primarily dependent on the fraction of the dose that is absorbed (f); the rates of absorption, metabolism, and distribution from the blood into the tissues; and the extent of distribution out of the blood into the tissues. For theophylline, the absorption is essentially complete (f = 100 percent) and rapid (1 to 2 hours) if the product used is not a sustained release preparation. The rate of distribution into the tissues is rapid enough that,

for all practical purposes, it can be assumed to be instantaneous; and the rate of theophylline metabolism is usually slow enough (in relation to the rate of absorption) that it can be ignored when calculating the peak serum concentration following a nonsustained release preparation.

Volume of Distribution (Vd)

The extent of distribution, usually expressed as the volume of distribution (Vd), is highly variable and may contribute significantly to the degree of fluctuation between the highest (peak) and lowest (trough) serum concentrations during a given dosing interval. The volume of distribution (Vd) is simply the theoretical volume of serum that would be required to hold all of the drug that is in the body at the given serum concentration. In other words, if the patient's serum concentration is 10 μg/mL (or mg/L) after a single, initial dose of 500 mg, then the Vd is 50 L (500 mg divided by 10 mg/L). Fifty liters of serum would be required to contain the 500 mg at the concentration of 10 μg/mL (or mg/mL). Alternatively, if the Vd and serum concentration (Cp) are known, then the total amount of drug in the body (total body stores or TBS) can be calculated by multiplying the volume of distribution (Vd) times the serum concentration (Cp) (Eq. 1: TBS = Vd × Cp).

Elimination Rate Constant (Kel) and Serum Half-Life (t 1/2)

Once a given peak serum concentration has been achieved, the rate of decline is determined by the elimination rate constant (Kel) or the serum half-life (t 1/2). Although the half-life (t 1/2) is readily recognized as the time required for the serum concentration to decrease by one-half, the elimination rate constant (Kel) is not always clearly or completely understood. The elimination rate constant (Kel) simply defines the fractional decline that will be seen in the serum concentration over a given time interval (usually 1 hour). If the serum concentration decline is plotted on a logarithmic scale, it will produce a straight line (i.e., linear), and the slope of that line is the elimination rate constant (Kel). This value can be calculated using the natural log of appropriately collected serum concentrations. Although this formerly required the clinician to look up the natural log of the serum concentration in a table of natural log values, many inexpensive calculators now have a natural log key for rapid determination of such values. Subtracting the natural log (ln) of two consecutive serum concentrations (not altered by additional drug administration) and dividing the result by the time (T) that elapsed between the two serum concentration determinations will yield the elimination rate constant (Eq. 2: Kel = [ln Cp1 − ln Cp2]/Change in T). Because the elimination rate constant (Kel) and serum half-life (t 1/2) are describing the same rate phenomena, they are inversely related in a constant fashion. The greater the elimination rate constant (Kel), the more rapid the serum concentration decline, and the shorter the serum concentration half-life (t 1/2). Because of this constant relationship, the product of these two terms (elimination rate constant and serum concentration half-life) will always equal a constant, 0.693, so that knowing one value allows the calculation of the other. Knowing the t 1/2 is important because of the basic fact that a period of five times the t 1/2 is required from the time a given dosage regimen is initiated until the patient stops accumulating the drug and reaches a steady-state serum concentration. At this point, the average serum concentration during each dosing interval (the mean steady-state concentration, or Cpss) is constant, and the amount of drug eliminated each day is the same as the daily dosage. This principle of serum concentration accumulation also applies following a change in a previously stable dosage regimen.

Clearance (Cl)

Clearance (Cl), another way of describing drug elimination, is the conceptual volume of serum from which all of the drug would be eliminated within a given period of time. If the patient is at steady-state conditions on a daily dosage of 1,000 mg, then the body must eliminate 1,000 mg per day as well. If the steady-state serum concentration (Cpss) is 10 mg/L, then the clearance is 100 L/day (100 liters of serum at a concentration of 10 mg/L must be completely cleared of drug each day if the Cpss is to remain stable). This total body clearance may be separated into hepatic clearance or renal clearance in some cases, but for routine dosing calculations, the total body clearance is most important (Eq. 3: Cpss = f × Dose/Cl, where f is the fraction of the dose absorbed). Additionally, because clearance can be mathematically correlated with the elimination rate constant (Kel) and volume of distribution (Vd)

(Eq. 4: Cl = Kel × Vd), knowing two of these values will allow the calculation of the third.

Solving the Patient's Problem

The major reason for reporting the described patient is to illustrate how the few basic principles and equations outlined above can be used in a practical fashion to maximize the information obtained from serum drug concentrations. The patient presented a therapeutic dilemma in that on three different occasions her asthma was well controlled by intravenous aminophylline infusions that produced remarkably predictable serum theophylline concentrations. Oral regimens, even while the patient was hospitalized, produced widely variable serum concentrations that were accompanied by either exacerbation of asthma or signs and symptoms of toxicity. Although variable absorption was suspected initially, a pharmacokinetic analysis of her serum theophylline concentrations suggested the possibility of sporadic compliance.

Because she did not receive additional doses following her admission theophylline value of 41 μg/mL, the subsequent values of 32 and 22 μg/mL allowed the calculation of an elimination rate constant (Kel). Subtracting the natural log of any two of these three values and dividing the result by the number of hours that elapsed between the respective sample collections produced an estimated elimination rate constant (Kel) of approximately 0.06/hour (Eq. 2: Kel = [ln Cp 1 − ln Cp 2]/Change in T). This Kel allowed the calculation of a serum half-life of 11.5 hours (Eq. 5: t 1/2 = 0.693/Kel). These calculations can be confirmed by noting that the decline from 41 μg/mL to 22 μg/mL (a decrease by almost half) took almost one half-life (11.5 hours).

During the most recent hospitalization, the four serum concentrations, which were drawn approximately 12 hours apart during the continuous infusion, did not demonstrate any accumulation of the drug and, therefore, were considered to indicate mean steady-state concentrations (Cpss) of approximately 14.8 μg/mL. Because the mean steady-state concentration is equal to the fraction (f) of the dose absorbed divided by the total body clearance (Eq. 3: Cpss = f × Dose/Cl), total body clearance (Cl) of theophylline was calculated to be 0.062 L/kg/hr (Cpss of 14.8 = f of 1 × a dose of 0.92 mg/kg/hr divided by a Cl of 0.062 L/kg/hr). Because clearance (Cl) is equal mathematically to the product of the elimination rate constant (Kel) and the volume of distribution (Vd) (Eq. 4: Cl = Kel × Vd), the Cl and Kel were used to calculate a Vd of 1.03 L/kg of ideal body weight (Eq. 4).

Although the patient's clearance (Cl) and volume of distribution (Vd) were outside of the usual population estimates (discussed below), these values were confirmed on more than one occasion and, ultimately, proved useful in solving the question of why her theophylline levels varied so greatly during oral therapy. When levels of less than 2 μg/mL were followed by a patient-requested stat level of 33.4 μg/mL, the possibility of sporadic compliance was reconsidered. Multiplying her serum concentration of 33.4 μg/mL by her volume of distribution (Vd) of 1.03 L/kg of ideal body weight × ideal body weight of 56.5 kg indicated that she had almost 2,000 mg of theophylline in her body (Eq. 1: TBS = Cp × Vd). Curiously, this was almost exactly the amount of theophylline that the medication record indicated had been administered to her since changing from the intravenous to the oral route. Apparently, she had failed to take her medicine when administered and had saved each dose and ingested them all at one time. These considerations led the clinicians to change to a liquid dose that was administered in the presence of the nurse and followed by a glass of water. This method of administration, which was initiated in an attempt to enforce compliance, produced therapeutic serum concentrations consistent with predictions based on her pharmacokinetic parameters. Furthermore, the difference between consecutive predose trough and postdose peak serum concentrations were consistent with the degree of increase that was expected based on the dose and the patient's estimated volume of distribution (i.e., the incremental change was equal to the dose divided by the volume of distribution [Vd] Eq. 6). These observations provided further substantiation that the estimated volume of distribution (Vd) was accurate. Additionally, it should be noted that acute ingestion of 2,000 mg of theophylline by a patient of this size with a usual volume of distribution (Vd) would have produced a serum theophylline concentration of approximately 80 μg/mL (2,000 mg dose divided by the Vd of 0.45 L/kg × 56.5 kg ideal body weight). It would appear, therefore, that her unusually large volume of distribution (Vd) prevented such sporadic

compliance from producing a potentially fatal level of toxicity.

Theophylline and Obesity

The average volume of distribution (Vd) for theophylline is 0.45 L/kg, with a range of 0.3 to 0.74 L/kg of ideal body weight. The mean theophylline half-life (t 1/2) for otherwise healthy nonsmoking adult asthmatics is 8.2 hours, with a usual range of 6.1 to 12.8 hours.[2,10] This patient's serum half-life (t 1/2) of 11.5 hours was slightly prolonged, although it was within the normal range, as was her elimination rate constant (Kel). Total body clearance (Cl), a product of the elimination rate constant (Kel) and the volume of distribution (Vd), reflects theophylline removal from the body and is a better predictor of dosage requirements. Although the mean value in nonsmoking adults is 0.039 L/kg/hr,[10] this patient's unusually large volume of distribution (Vd), together with a normal elimination rate constant (Kel), produced an unusually rapid theophylline clearance of 0.062 L/kg/hr. The reason for her large volume of distribution (Vd) is not clear. One possible explanation is her obesity. The effect of obesity in altering the pharmacokinetics of theophylline is controversial. Potential pharmacokinetic differences in obesity may occur in drug distribution, biotransformation, and excretion. Distribution may be altered due to a decrease in the proportion of body water and muscle mass, as well as the increased proportion of fat to total body weight. Increased total blood volume and cardiac output may increase renal and hepatic blood flow and thereby alter the rate of biotransformation and excretion. Changes in plasma protein binding also may occur due to increased frequency of hyperlipidemias observed in obese patients.[11]

Despite these possible changes in pharmacokinetics, clinical trials have produced conflicting results on whether total body weight or ideal body weight is more appropriate for determination of theophylline dosing.[12,13] Conflicting properties of theophylline also make it difficult to predict its distribution into fat. The usual slight solubility of theophylline in ether, chloroform, and alcohol suggest that it should not distribute into fat; but the water partition coefficient (logP = −0.02) favors distribution into adipose tissue.[2]

Although obesity and/or changes in serum protein binding of theophylline may alter the volume of distribution (Vd), the daily dosage requirements will remain unchanged if clearance (Cl) is not altered. Even though the volume of distribution (Vd) and clearance (Cl) are mathematically related (Eq. 4: Cl = Kel × Vd), a change in one usually does not produce a change in the other because of an offsetting change in the elimination rate constant (Kel). An increase in the volume of distribution (Vd) typically reflects a shift of the drug out of the vascular space where it is less available for elimination; consequently, the elimination rate constant (Kel) is reduced. The increase in Vd is, therefore, accompanied by a corresponding decrease in Kel, so that Cl remains unchanged (Eq. 4: Cl = Kel × Vd). In our patient, however, the unusually large Vd was not associated with a low Kel. Clearance (and daily dosage requirements), therefore, were higher than normal.

Erratic Absorption of Theophylline

Another potential problem with theophylline dosing that must be considered is erratic absorption. Theophylline is rapidly and completely absorbed from liquid preparations and plain uncoated tablets, but these formulations result in greater peak-to-trough fluctuations.[6] Slo-Phyllin™, an uncoated tablet, produced a peak theophylline level of 21 μg/mL in this patient but was associated with intolerable nausea and diarrhea. Choledyl™, an enteric-coated, rapid release theophylline product, which also was prescribed, has been reported to have erratic dissolution and may result in a significantly decreased rate or extent of absorption.[14,15] Although the potential problem of erratic absorption of theophylline had to be considered in this patient, the degree of change in absorption that would have been necessary to explain her serum level fluctuations would be extremely unlikely.

Slow release formulations of theophylline differ in the rate and extent of absorption, and these differences are sometimes seen between different dose sizes of the same brand. Theo-Dur™ is absorbed fairly completely and at a constant rate with minimal peak-to-trough fluctuation when given every 12 hours.[6,15] Even with this product, patients with extremely rapid elimination (e.g., t 1/2 < 2 hours) will require more frequent dosing intervals. Even though the theophylline t 1/2 in this patient was 11.5 hours, the apparent administration of Theo-Dur™ every 6 hours still failed to produce therapeutic theophylline concentrations. Because the variability in the serum concentra-

tions was greater than could be explained reasonably by variability in absorption, sporadic compliance had to be considered.

Conclusion

This case illustrates the dilemma of distinguishing between erratic absorption and noncompliance. Because of the variability in theophylline pharmacokinetics, some patients may fail to achieve a therapeutic peak concentration of theophylline following usual doses. Although it is reasonable to suspect a problem with absorption, other factors to consider include rapid elimination and noncompliance. Noncompliance is often considered in out-patients with low serum concentrations, but it may be overlooked in the hospitalized patient. The patient very convincingly led her clinicians to suspect that there was an absorption problem. The use of appropriately timed serum assays and the application of pharmacokinetic principles, however, produced information that strongly supported sporadic compliance, which was confirmed by levels following a change to an enforced method of administration.

References

1. Bussey HI, Hoffman EW. A prospective evaluation of therapeutic drug monitoring. Ther Drug Monit 1983; 5:245-8.
2. Hendeles L, Massanger, Weinberger M. Theophylline. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics: Principles of therapeutic drug monitoring. Spokane WA: Applied Therapeutics, 1986:1105-88.
3. Jenne JW, Wyze MS, Rood FS, MacDonald FM. Pharmacokinetics of theophylline. Application to adjustment of the clinical dose of aminophylline. Clin Pharmacol Ther 1972; 13:349-60.
4. Upton RA, Thiercelin JF, Guentert TW, et al. Intraindividual variability in theophylline pharmacokinetics: statistical verification in 39 of 60 healthy young adults. J Pharmacokinet Biopharm 1982; 10:123-34.
5. Weinberger M, Hendeles L, Wong L. Relationship of formulation and dosing interval to fluctuation of serum theophylline concentrations in children with chronic asthma. J Pediatr 1981; 99:145-52.
6. Hendeles L, Iafrate RP, Weinberger M. A clinical and pharmacokinetic basis for the selection and use of slow release theophylline products. Clin Pharmacokinet 1984; 9:95-135.
7. Upton RA, Thiercelin JF, Guentert TW, et al. Evaluation of the absorption from some commercial sustained-release theophylline products. J Pharmacokinet Biopharm 1980; 8:131-49.
8. Pollack GM, Baswell B, Szefler S, Shen DD. Comparison of inter- and intra-subject variation in oral absorption of theophylline from sustained-release products. Int J Pharmaceutics 1984; 21:3-16.
9. Hendeles L, Weinberger M, Wyatt R. Guide to oral theophylline therapy for the treatment of chronic asthma. Am J Dis Child 1978; 132:876-80.
10. Hendeles L, Weinberger M, Bighley L. Disposition of theophylline after a single intravenous infusion of aminophylline. Am Rev Respir Dis 1978; 118:97-103.
11. Zell M, Curtis RA, Troyer WG, Fischer JH. Volume of distribution of theophylline in acute exacerbations of reversible airway disease. Effect of body weight. Chest 1985; 87:212-6.
12. Gal P, Jusko WJ, Yurchak AM, Franklin BA. Theophylline disposition in obesity. Clin Pharmacol Ther 1978; 23:438-44.
13. Rohrbaugh TM, Danish M, Ragni MC, Yaffe SJ. The effect of obesity on apparent volume of distribution of theophylline. Pediatr Pharmacol 1982; 2:75-83.
14. Upton RA, Powell JR, Guentert TW, et al. Evaluation of the absorption from some commercial enteric-release theophylline products. J Pharmacokinet Biopharm 1980; 8:151-64.
15. Weinberger M, Hendeles L, Bighley L. The relation of product formulation to absorption of oral theophylline. N Engl J Med 1978; 299:852-7.

Appendix*

Eq. 1: TBS = Cp × Vd

Eq. 2: Kel = (ln Cp 1 − ln Cp 2)/Change in T

Eq. 3: Cpss = f × Dose/Cl

Eq. 4: Cl = Kel × Vd

Eq. 5: T 1/2 = 0.693/Kel

Eq. 6: Change in Cp = Dose/Vd†

*Cl = Clearance; Kel = elimination rate constant; f = fraction of dose absorbed; t 1/2 = serum elimination half-life; lnCP = natural log of serum concentration; Change in T = time difference between sample collections; Change in Cp = change in serum concentrations before and after absorption of an oral does; Vd = volume of distribution; Cp = serum concentration; Cpss = serum concentration at steady-state; TBS = total body stores or total amount of drug in the body.

†This equation assumes instantaneous drug absorption and distribution and does not allow for the drug elimination that occurs during the absorption time.