Title: Computer Simulated Theophylline Kinetics

Authors: P.G. Boysen, M.D., J.D. Robinson, Pharm. D., S. M. Lupkiewicz, M.S.

Affiliation: Departments of Anesthesiology and Internal Medicine, College of Medicine, and College of Pharmacy, University of Florida and Veterans Administration Medical Center, Gainesville, Florida 32602

Introduction. To demonstrate pharmacokinetic principles to students and housestaff we devised a computer program for use as an instructional aid.1 The program was designed for a specific drug (theophylline) but can be adapted for other drugs. It displays data in both a tabular and graphic form and performs calculations. In addition, recommendations are made for intermittent oral dosing or continuous intravenous infusion. These data and calculations were obtained after a single intravenous dose of the drug. The program has since been expanded to describe the extent and rate of drug accumulation when repeated doses of the drug are administered at specified intervals. These principles are of obvious importance since it closely approximates many clinical situations.2,3

Materials and Methods. Data were accumulated from ten subjects including normal volunteers, asthmatics, and patients with chronic airway obstruction. Informed consent was obtained and the study was approved by the Health Center Committee for the Protection of Human Subjects. A single dose of aminophylline (85% theophylline) was calculated at 5.6 mg/kg and administered intravenously in 30 cc D5W over 20 minutes. A minimum of eight samples were drawn through an indwelling intravenous catheter. Timing of sample collection was planned to define both the distribution and elimination phase of the drug since it follows a two-compartment model. Theophylline levels in micrograms per milliliter were measured using a radioimmunoassay technique. These data are then entered into the program in table form. A time vs. log serum concentration graph is then displayed and multiple calculations are performed. These include the elimination slope (b) and ordinal intercept (B), the distribution slope (a) and ordinal intercept (A), the beta half-life (tβ), drug concentration at 0 time (Cp0) and the volume of distribution of the drug (Vd) by calculating the area under the curve. A continuous infusion dose and intermittent dosing regimen is then suggested. In order to test the recommendations and observe anticipated peak and trough blood levels a regimen can then be selected, be graphic analysis of serum drug level vs. time is charted.

Results. The graph below depicts a simulated analysis for an individual patient being treated with theophylline for severe chronic bronchitis. An initial 370 mg of aminophylline was given as an intravenous bolus, resulting in a serum theophylline level of 14 μg/mL. The tβ is 4.93 hours and the Vd was .50 L/kg. Based on these calculations a continuous infusion of 68 mg per hour was recommended to maintain a blood level of 15 μg/ml at steady state. An oral maintenance dose of 250 mg at four hour intervals should result in peak blood levels of 18 μg/ml and trough levels of 13 μg/ml. Alternatively, if an oral regimen of 500 mg at eight hour intervals were instituted one might expect peak levels of 22 μg/ml and trough levels of 8 μg/ml.

Discussion. This example illustrates several important principles. Firstly, it shows the rationale for using a bolus dose for a medication to rapidly achieve therapeutic blood levels of the drug. Secondly, when appropriately administered it demonstrates the advantage of a continuous infusion of a drug in acute situations where therapy must be tightly controlled. Lastly, the advantage of administering a therapeutic dose of a drug near the elimination half-life is obvious. Doubling the dose and doubling the dosage interval results in peak blood levels in the toxic range and trough blood levels that are subtherapeutic. Similarly, the program can display the effect of varying dosages and dosing intervals on drug accumulation under any regimen the student chooses. These principles apply not only to theophylline but to many drugs used in the OR and ICU environment such as narcotics, lidocaine, aminoglycosides, etc.

Supported by Health Services Research and Development, Veterans Administration.

References: