Title : PHARMACOKINETICS OF THEOPHYLLINE: A TWO-COMPARTMENT INSTRUCTIONAL MODEL

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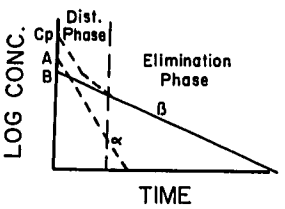
Introduction. Pharmacokinetics is the quantitative study of drug disposition in the body. Knowledge of pharmacokinetics has greatly improved drug therapy in recent years. Familiarity with basic pharmacokinetics is increasingly important to the practice of anesthesiology. Identical doses of a drug administered to two different patients may result in an inadequate response in one and toxic side effects in the other. When administered intravenously the plasma levels of a drug depend mainly on volume of distribution and rate of elimination. The optimum dose of a drug is achieved when a desired therapeutic response is obtained and adverse effects are minimized. We selected theophylline to demonstrate basic pharmacokinetic principles to fellows and senior residents because (1) accurate plasma levels are rapidly available using a radioimmunoassay technique and (2) plasma theophylline levels have been shown to correlate with therapeutic effect of the drug.

Materials and Methods. To facilitate calculations, a computer program was developed with the capacity for graphic display and estimation of dosage regimens. An infusion of 375 mg of Aminophylline (85% theophylline) in 50 cc D5W was administered intravenously to four subjects over 20 minutes. Informed consent was obtained and this study was approved by the Health Center Committee for the Protection of Human Subjects. A minimum of eight samples (four during the distribution phase, four during the elimination phase) were drawn through an indwelling venous catheter over an eight hour period. Theophylline levels in micrograms/milliliter were measured using the radioimmunoassay technique. The computer program was developed to determine the distribution and elimination rates using a two-compartment model[1,2]. Theophylline levels and time of sampling are entered into the program and represented in both table and graph form. The regression line for the elimination phase (β) is computed by the method of least squares. The regression line for the distribution phase (α) is obtained by extrapolating the elimination curve back to time zero, and resolving the curve into two components by subtracting values on the β-slope from measured theophylline levels. Beta half-life ($t_{\frac{1}{2}\beta}$) is the natural log of 2 divided by the β-slope. Drug concentration at time zero (Cp^0) is obtained by adding the ordinal intercepts of the distribution phase (A) and the elimination phase (B).

BLOOD LEVEL vs TIME



Results.

Subject	Hgt-Wgt	Cpk	Vd	β-slope	$t_{\frac{1}{2}\beta}$
1. 35.M	70"-160#	25.9	41.5L	.11	6.25
2. 28.M	67"-147#	15.7	30.5L	.08	9.0
3. 25.F	69"-145#	18.6	40.6L	.07	10.4
4. 28.F	67"-118#	11.1	51.0L	.06	11.6

These data demonstrate the variability of the volume of distribution and rate of elimination common to clinical practice. Since the volunteers were normal, no abnormalities in liver function or cardiac function(either of which would alter the $t_{\frac{1}{2}\beta}$) were present.

Discussion. This mathematic program will apply to any drug which admits a two-compartment model. These principles are important for intelligent intravenous dosing with many drugs such as narcotics, lidocaine, digitalis, aminoglycosides, etc. Administration of an initial bolus of a specific drug, dose and dosing intervals, and continuous infusions can be appreciated when decisions are based on pharmacokinetic principles. The therapeutic range of plasma theophylline levels is 10-20 μg/ml. Based on a target plasma concentration and bodyweight, a continuous infusion rate can be calculated. Alternatively, a recommended IV bolus dose (based on the volume of distribution of the drug) and a dosing interval (based on calculation of the plasma half-life) can be estimated. The use of this program, which eliminates tedious mathematics and focuses on interpretation of a graphic display is a useful method to emphasize basic principles in a manner that makes pharmacokinetics both interesting and relevant.

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References.

1. Hug CC, Jr: Pharmacokinetics of drugs administered intravenously. Anesth Analg 57: 704-723, 1978

2. Greenblatt DJ, Koch-Weser J: Clinical pharmacokinetics. N Engl J Med 293: 702-705, 964-970, 1975