Nonparametric Approach to Population Pharmacokinetics in Oncology Patients Receiving Aminoglycoside Therapy

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A nonparametric expectation maximization approach to the study of population pharmacokinetics is described for an aminoglycoside antibiotic. The method is used to explore population estimates for gentamicin clearance (liters per hour per creatinine clearance) and volume of distribution (liters per kilogram) in tumor patients. Joint and marginal probability distributions are plotted and further characterized by using standard descriptors such as mean, median, mode, standard deviation, skewness, and kurtosis. Results of additional analyses using hematologic or solid tumor subpopulations agree with those of a recent larger study which found no significant pharmacokinetic differences between these groups. Nonparametric maximum-expectation analyses are convenient and allow exploratory analysis of population estimates directly from routine laboratory information.

Bayesian feedback methods bring population (a priori) information into pharmacokinetic decisions with a demonstrable advantage (9, 10). However, for economic and ethical reasons, these estimates did not become easily uncovered until the introduction of techniques capable of analyzing routine patient data (3). A nonparametric expectation maximization (NPEM) algorithm is one method capable of population analyses under potentially austere conditions (e.g., when there are as few as one or two drug concentrations per subject) (2, 6, 7).

Tumor patients may represent a pharmacokinetically distinct subset of individuals receiving aminoglycoside antibiotics. Previous reports describing larger than expected parameters in neutropenic subjects with solid or hematologic malignancies have been critically reviewed in a recent study (1). However, these investigations employ traditional methods of statistical inference which are known to work best under somewhat exacting assumptions. On the other hand, the more robust techniques of exploratory data analysis offer an informal way of quickly exploring such differences unencumbered by the restrictions of classical techniques (4). This approach (largely developed by J. W. Tukey) inspects the structure of data in a flexible manner and often suggests the outcome of subsequent tests of statistical inference. This report describes our attempt to clarify gentamicin pharmacokinetics in a population study of oncology subjects using NPEM for exploratory data analysis.

MATERIALS AND METHODS

Data collection. During the first 6 months of 1992, 28 febrile neutropenic patients, each receiving a single course of antimicrobial therapy, were monitored under a protocol developed by the Department of Pharmaceutical Services, University of California, Davis Medical Center, Sacramento. Standard demographic and laboratory information was collected and utilized to maintain gentamicin peak concentrations (obtained 1 h after the start of infusion) of between 5 and 10 μg/ml and predose levels of less than 2 μg/ml. There were 10 males and 5 females with underlying hematologic malignancies (14 with leukemia) as well as 2 males and 11 females with solid tumors at various stages of treatment. The means and standard deviations for age (48.5 and 17.0 years) and weight (61.5 and 12.5 kg) indicate a broad range of values for this study population. An average of 3.6 gentamicin levels per patient (range, 2 to 5) were measured during the first week of therapy by using fluorescence polarization immunoassay (TDx; Abbott Diagnostics Division). During this time, serum creatinine levels (mean = 0.9 mg/dl; standard deviation = 0.2) remained stable and within normal limits. In an effort to reduce statistical noise, dose and concentration records were carefully documented by a member of the department familiar with the protocol. Furthermore, each lot of gentamicin was assayed, and doses were adjusted to account for potentially significant interlot variations from the labeled concentration (8). As required by NPEM, the concentration-dependent assay error was explicitly defined (5) and utilized in the analysis for weighting gentamicin concentrations. (For our laboratory this was defined as standard deviation = 0.0519 + 0.0428C + 0.0137C², where C is the concentration in micrograms per milliliter.)

Analyses. An NPEM algorithm available from the Laboratory of Applied Pharmacokinetics, University of Southern California (6), was used to described the distribution of several pharmacokinetic parameters. The NPEM algorithm employs a statistical technique of expectation and maximization in a novel approach which initially estimates the likely distribution of a pharmacokinetic parameter rather than the parameter itself. Following this, standard statistical descriptors of the parameter, including the mean, standard deviation, and coefficient of variation, are estimated. The probability distribution for each parameter is visually described with joint and marginal density plots as well as numerically with standard descriptors (skewness, kurtosis, mode, median, and first and third quartiles). Covariance and correlation coefficients are provided as estimates of the strength of the relationship between parameters. Lastly, a log likelihood statistic describes the model's fit. NPEM allows any one of nine choices of paired parameters to be analyzed during a single session. The most familiar of these include the elimination rate constant, the clearance, the volume of distribution, and the slopes of these values with respect to creatinine clearance (CLCR) (for the elimination rate constant and for

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clearance (CS) or weight (for the volume of distribution [VS]). For this study two parameters were selected: VS (liters per kilogram) and CS (liters per hour per CLCR, where CLCR is measured in milliliters per minute per 1.73 m²). NPEM allows any user-defined intercept for the gentamicin-versus-CLCR relationship. Minimal nonrenal clearance was assumed by setting the intercept at 0.0025 liter/h. The data were then divided into two groups and reanalyzed to explore possible pharmacokinetic differences between hematologic and solid malignancies.

RESULTS

For each pharmacokinetic parameter, NPEM provides statistical summaries (Table 1) and plots which together offer a detailed view of the parameter’s distribution. In Fig. 1 the joint and marginal distributions for VS and CS are reproduced. Volumes of distribution for the full and divided data show some peakedness (kurtosis) and a small to modest amount of positive skewness. In all three analyses, the distribution for VS appears to approximate a normal curve with a mean in the neighborhood of 0.3 liter/kg. From an exploratory data analysis standpoint, VS appears unaffected by the diagnosis of hematologic versus solid malignancy (Fig. 2). Numerically, the distributions for CS exhibit some peakedness and minimal skewness. In Fig. 1, the CS marginal distribution suggests the possibility of two adjoining subpopulations separated at a value near 0.05 liter/(h · CLCR). After the data are divided into hematologic-tumor and solid-tumor categories, NPEM raises the possibility of a small difference in mean values (0.059 and 0.049 liter/[h · CLCR], respectively) but not without a moderate degree of spread (as seen in the standard deviation and coefficient of variation). Overlaying the individual marginal distributions (Fig. 2) makes this visually apparent.

DISCUSSION

As seen from the perspective of exploratory data analysis, NPEM provided extensive information regarding the likely distributions of two important pharmacokinetic parameters. Measures of skewness and kurtosis indicated some departure from normality, and had this been extreme, pharmacokinetic monitoring using medians and the interquartile range (specifically the interquartile range/1.35) could replace means and standard deviations. Estimates of covariance and correlation for the joint (CS-VS) distributions were furnished, but of these, only the correlation is unitless and directly interpretable. The analysis for VS uncovered a somewhat symmetric, unimodal distribution with a mean and range in close agreement with those in a recent study of 880 subjects by Bertino et al. (1). Graphic exploration of CS suggested a multimodal distribution, and as in the study of Bertino et al., the mean gentamicin clearance for our patients with leukemia was about 20% higher than for subjects with other malignancies. However, further NPEM graphic and numeric analyses disclosed considerable overlap in

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<th>TABLE 1. NPEM population estimates of CS and VS</th>
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<sup>a</sup> CS is measured in liters per hour per CLCR; VS is measured in liters per kilogram.
<sup>b</sup> Covariance = -0.0005; correlation = -0.037; log likelihood = -503.
<sup>c</sup> Covariance = -0.0002; correlation = -0.146; log likelihood = -216.
<sup>d</sup> Covariance = 0.0002; correlation = 0.286; log likelihood = -272.

FIG. 1. Joint and marginal probability density functions for gentamicin VS and CS in 28 neutropenic patients with hematologic or solid malignancies.
these two populations, suggesting (as in the study of Bertino et al.) a small, inconsistent difference.

Unlike a traditional confirmatory study, an exploratory analysis by NPEM does not rest on strict statistical requisites. For example, the requirement for normality encountered by the study of Bertino et al. (prior to analysis by $t$ tests and analysis of variance) is avoided. Similarly, unlike the latter investigation, the NPEM approach did not require writing a logistic model with leukemia as the dependent variable (implying that the pharmacokinetic parameters had some diagnostic value).

The matter of sample size is more difficult to address, since statistical power is not strictly at issue with exploratory data analysis. In a previous report using NPEM, reexamining a complement of 20 subjects from a prior study of 71 patients provided nearly identical summary statistics (2). However, population methods operating under conditions of sparse data do require a particular focus on accuracy during the collection phase. NPEM solicits precise definition of the laboratory assay error, and we undertook the additional precaution of adjusting gentamicin doses with respect to interlot discrepancies (approximately 10%). At this time NPEM accepts only an intravenous one-compartment body model, although a two-compartment model is under development.

The value of population pharmacokinetics rests largely on the ability of these methods to contribute a priori information to subsequent Bayesian-like analyses. The intent of the population analysis is to accomplish this task from sparse, routine data that are often unusable in a traditional investigation. In this respect, NPEM offers one approach to a population study by providing a detailed exploration of fundamental properties.

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REFERENCES


FIG. 2. Comparison of marginal probability density functions in hematologic (--) versus solid (-----) malignancies for VS and CS.