ACHIEVING CONCENTRATION GOALS WITH NONPARAMETRIC COMPARTMENTAL MODELS - THE "MULTIPLE MODEL" DESIGN OF DOSAGE REGIMENS.

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ABSTRACT

Multiple model (MM) design and stochastic control of dosage regimens permits essentially full use of all the information contained in either a nonparametric EM (NPEM) population pharmacokinetic model or in an MM Bayesian updated parameter set, to achieve and maintain selected therapeutic goals with optimal precision (least predicted weighted squared error). The regimens are visibly more precise than those developed using mean parameter values. Bayesian feedback has now also been incorporated into the MM software. An evaluation of MM dosage design using an NPEM population model versus dosage design based on conventional mean population parameter values is presented, using a population model of Vancomycin. Further feedback control was evaluated, also incorporating realistic simulated uncertainties in the clinical environment such as those in the preparation and administration of doses.

INTRODUCTION

Previous work from this laboratory has shown the utility of NPEM population pharmacokinetic modeling, resulting in a discrete number of support points for the entire population joint probability density function, compared to that using conventional single point parameter estimates such as means and variances, as are obtained from parametric population models [1]. These multiple NPEM support points become multiple contending parameter estimates, instead of the conventional single point parameter estimates, to use to plan the initial dosage regimen for a new patient who appears to belong to that population.

Figure 1 shows an example of the multiple support points for the joint probability density for a population pharmacokinetic model of Vancomycin. There are a total of 28 such support points, derived from the population of 30 patients studied. Each support point has a discrete value for each of the 4 pharmacokinetic parameter values - the central compartment apparent volume of distribution (Vd), the increment of elimination rate constant per unit of creatinine clearance (Kslope), and the rate constants from the central to the peripheral compartment (Kcp) and back from it (Kpc). Each support point is a collection of the estimated values for each parameter, along with an estimate of the probability for that support point. The collection of all such points (28 in the present case) is the estimate of the discrete joint probability density for the population, and is made without making any assumptions about the overall shape of that distribution as is done with parametric methods which obtain only estimates of the means and variances of the parameters, which are also easily obtained from the NPEM overall density. The NPEM population model is thus represented not by a single best parameter estimate such as mean or standard deviation (SD),
but rather by a matrix of rows and columns. The 5 columns represent the discrete values of the 4 parameters Vd, Kslope, Kcp and Kpc, and the probability associated with each support point.

In the present model, there were 28 rows of 5 columns each. The 28 rows provided 28 possible versions of the next patient for whom the population model served as the Bayesian prior for the optimal design of the initial dosage regimen to achieve the desired target goal. These multiple points are shown graphically in Figure 1, for the parameters of Vd and Kslope. A similar 3D plot can be made for Kcp and Kpc, and for any desired pair of parameters.

This report further describes a comparison of the results achieved using the full NPEM population model versus results obtained using the traditional method based on mean Vancomycin population parameter values, with respect to the ability of each regimen to achieve and maintain the chosen serum level goal(s). Note that the MM regimen is specifically computed to minimize the expected value of the total weighted squared error in the achievement of the goal(s), while the traditional regimen using single point parameter estimates cannot do this at all.

The MM software has now been extended to incorporate feedback as well. This report also describes a realistic simulation of vancomycin therapy in which common errors are present in the preparation of the doses and in their timing, as well as in the measurement of the serum levels. These mean clinical error values are also known to the MM controller for designing the dosage regimen with appropriate skepticism.

The natural link between nonparametric population modeling and optimal drug therapy is the MM approach to dosage design. In contrast, the limiting factor in parametric population modeling is that there is only one single possible value for each parameter. Using parametric population models, after the therapeutic goal is clinically selected, there is only one regimen to compute, that which controls the single chosen version or model of the patient, using the mean, median, or modal parameter values, exactly. There is no opportunity to consider the fact that the patient actually might not have that exact model of the behavior of the drug.

In contrast, when one uses nonparametric population models as the Bayesian prior for designing the initial dosage regimen, there are many (multiple) possible models or versions of the patient which one can use, one for each support point in the discrete joint distribution. Each support point has its own probability of representing the patient. A candidate regimen can be given to each support point, with its own individual parameter values, and the probability associated with that point, and future serum concentrations can be predicted using the parameter values for each support point, and its probability. In this way, an entire family of serum concentrations can be predicted into the future. At the time the chosen goal is desired, it can be compared with the many serum concentrations predicted to occur at that time (one from each support point), and the weighted squared error with which the goal fails to be achieved can be computed. Other candidate regimens can also be examined.

The optimized regimen chosen is the one which specifically minimizes the weighted squared error in the achievement of the goal. In this way, the "multiple model" (MM) regimen has the new feature of being specifically designed to achieve the goal with the greatest possible precision for any set of population raw data (doses and serum levels) available up to that time, because it considers all the many possible versions or models of the patient, using the NPEM
population model, and the many different predicted serum concentrations, one from each support point, as shown below in Figures 3 and 4, instead of that using only the single most likely version [2].

Later on, as data of serum concentrations become available for feedback, Bayes' theorem is used to appropriately increase the probability of those support points or models that predicted the measured levels well, and to decrease the probability of those that did not. The revised Bayesian posterior joint distribution, usually consisting of fewer significant support points, is then used to reconstruct the family of serum level trajectories taking place during the past [3,4].

The bandwidth or diversity of these predicted trajectories reflects the confidence with which the joint distribution is known for each patient, and the degree of learning about that patient provided by the feedback from the serum level data. As always, the plot based on the past trajectories of serum levels is compared with the clinical behavior of the patient, the patient's sensitivity to the serum drug concentrations is reassessed, the target goal is re-evaluated, and a new regimen is again computed to achieve that goal, again with the greatest possible precision for all the information in the population model and the individual patient data which is available up to that time.

**THE POPULATION PHARMACOKINETIC MODEL OF VANCOMYCIN**

This 2 compartment model [5] was developed using the NPEN2 program in the USC*PACK PC clinical collection. Its parameters were \( V_c \), the apparent volume of the central (serum level) compartment, in L/kg; \( K_{cp} \), the rate constant from the central to the peripheral compartment; \( K_{cp} \), the rate constant in the reverse direction; and \( K_{slope} \), the increment of the elimination rate constant (\( K_e \)) for each unit of creatinine clearance (CCr), all in hr\(^{-1}\). A nonrenal component, \( K_{int} \), was fixed at 0.002043 hr\(^{-1}\). Thus the overall \( K_e = K_{int} + (K_{slope} \times CCr) \).

Data of 30 patients receiving Vancomycin were analyzed. The file containing the population joint probability density values (the 28 rows of parameter values and their probabilities) was read into the program for MM design of dosage regimens [3,4]. Table 1 shows the summary values of the various population parameters.

There were 28 support points for the population joint parameters. Each support point had a value for each parameter, representing a candidate model for the patient, and a computed probability. Figure 2 shows the 28 various support points by their index number (their parameter values are not shown) and their relative probabilities. The graphical plot of the relative values for \( V_c \) and \( K_{slope} \) is shown in Figure 1.

**THE SIMULATED CLINICAL SCENARIO FOR INITIAL THERAPY (DAY 1)**

A therapeutic goal of a stable serum vancomycin concentration of 15 ug/ml, to be achieved by continuous series of intravenous infusions at various rates, was chosen for this simulated study. While it is common to give vancomycin by intermittent IV infusion and to select a trough goal of 10 ug/ml, with peaks about 35 - 45 ug/ml, the stable goal of 15 ug/ml was selected here as a reasonable alternative goal, to be achieved at the end of an initial 2 hr loading infusion, again at the end of 2 subsequent 2 hr infusions during the distribution phase of this 2-
compartment drug, and at the end of 3 further infusions of 6 hrs each, to complete Day 1 of therapy. Thus the vancomycin was given by continuous IV in 3 infusion steps of 2 hrs each, followed by 3 steps of 6 hrs each, to achieve the goal of 15 ug/ml at the end of each infusion step.

THE TWO INITIAL REGIMENS COMPARED

Two types of dosage regimen to achieve the target goal of 15 ug/ml were developed and compared. One, the traditional type of regimen, was developed using the single point mean population NPEM parameter values shown in Table 1. It was designed to achieve the goal exactly, as there was only one exact value for each parameter to consider. No consideration of any therapeutic error is possible with this method of dosage design.

The other regimen, the MM regimen, used all the 28 support points of the NPEM Vancomycin population model in designing the regimen. It therefore took into account all these different models of the patient, each with its probability of "being" the new patient, to receive the initial regimen. The MM dosage designer thus faces the fact that what may be a correct regimen for a particular support point set of parameter values (such as the means), will inevitably be incorrect for all other parameter values, and develops the regimen which minimizes the overall error in the failure to achieve the desired target goal.

If the regimen based on the mean parameter values is given to each of the 28 support points or "multiple models" of the patient, each model will have its own predicted trajectory of serum levels over time, and each of these will contribute its increment of weighted squared error in its failure to achieve the target goal.

Figure 3 shows the resulting trajectories when the regimen to control the population model having the mean parameter values was given to all 28 support points or models of the patient. Many predicted serum concentrations were very high, as the distribution of the Vd was not at all Gaussian, but was skewed to the right. As shown in Table 1, the mean Vd was actually close to the 75th percentile. Due to all the variability in the various combinations of population parameter values, the variability in the serum level response was great.

In contrast, the other regimen, the MM regimen, was specifically designed to minimize the expected value of the total weighted squared error in achievement of the goal, specifically taking into account all the predicted 28 MM trajectories, each of which was weighted by its probability. Figure 4 shows the results of the MM regimen. The trajectories are much less variable, and are much better centered about the chosen goal of 15 ug/ml.

INCORPORATION OF CLINICAL ENVIRONMENTAL NOISE TERMS AND MM SERUM LEVEL FEEDBACK

The MM scenario has now been carried further, incorporating serum level feedback and Bayesian posterior updating of the probabilities (but not their values) of the 28 population model support points.

The capabilities of this control strategy were evaluated by Monte Carlo simulation of a realistic clinical scenario which also contained stated sources of simulated clinical environmental
errors in the preparation of the doses and the timing of their administration, as well as in the laboratory assay error. Each ideal computed dose was assumed to be prepared with a random Gaussian error having a standard deviation (SD) of 10% of the dose. That erroneous dose was then what was "given". Further, the times of switching from one IV infusion rate to another were assumed to have a random Gaussian error having a SD of 6 min for the start of the first 2 hr infusion step, and 12 min for the switch to each of the other infusion steps.

Three days of such simulated therapy were analyzed. Serum levels were assumed to be drawn exactly at 2, 4, and 8 hours into the regimen for each day. Their assay error was introduced as a random Gaussian error having the SD of the Abbott TDx assay used in our laboratory to make the original population model. This heteroschedastic random Gaussian assay error (see [6]) had an SD represented by the polynomial

\[ SD = 0.30752 + 0.024864C + 0.00027637C^2, \]

where C is the true serum level of the "true patient" (randomly chosen as support point number 15 in the model set) "drawn" at the various sampled times.

Thus two things were going on in this scenario. On the one hand, the MM stochastic controller was designing the MM stepwise infusion regimen to most precisely achieve the goal of 15 ug/ml at 2, 4, 6, 12, 18, and 24 hours during the first day of therapy. On the other hand, this ideal dosage regimen was being corrupted by the Monte Carlo simulator, incorporating the clinical errors stated above. The MM controller also takes these stated errors into account in designing the dosage regimen.

Figure 5 shows the computed 99% most probable trajectories of the serum levels for Day 1 of MM therapy, before any feedback. The variability is close to that shown is Figure 4. The solid lines represent the 95% most probable trajectories, and the dotted lines represent the next most probable 4%. This represents the clinical situation as it is knowable to the clinician until the serum level results come back.

Further, in a way that is never knowable clinically, the time course of the computed serum concentrations for the simulated "true patient" (here represented by support point #15, chosen randomly), is shown in Figure 6. Clearly there was visible error in the initial achievement of the therapeutic goals, as the true patient had parameter values different from those of the population mean values.

The true patient's serum level results at 2, 4, and 8 hrs into the regimen, corrupted by their assay errors, were made available at the end of Day 1. Based on these results, Bayesian updating of the multiple models was done, revising their probabilities using Bayes theorem, without changing the parameter values themselves. The results are shown in Figure 7. Only four support points now had significant probabilities, and the rest had negligible probabilities.

The events of therapy days 2 and 3 repeated the same format of Day 1. The goals again were 15 ug/ml, to be achieved at 2, 4, 6, 12, 18, and 24 hrs into each day's regimen. The same continuous infusion format of 3 steps of 2 hrs followed by 3 of 6 hrs was used. Serum levels were
again "obtained" at 2, 4, and 8 hrs into each day, with results available at the end of each day for revising the model probabilities and planning the next day's regimen.

Based on this, the regimen for day 2 was now computed and (with the corrupting clinical environmental errors) was given. Figure 8 now shows the 99% most probable serum level trajectories predicted for day 2 (horizon #2). As shown by the much narrower band of predicted serum concentrations for Day 2, one has learned a lot about the patient from the first set of serum levels. In addition, the response of the "true patient" was quite precisely controlled for Day 2, as shown in Figure 9.

At the end of Day 2, when the 3 new serum levels came back during Day 2, the model probabilities were further updated as shown in Figure 10. Three significant support points are present. These revised probabilities were used to plan the regimen for Day 3. Based on this, the regimen for day 3 was computed and given. Figure 11 shows the 99% most probable serum level trajectories. The controller (and thus the clinician) thinks it is doing just great. However, life is never quite so kind. Because of the stated errors in the clinical environment, the response of the "true patient" departed slightly from the predicted response, as shown in Figure 12, below.

Finally, after the three new simulated measured serum levels came back from Day 3, the revised model probabilities are shown in Figure 13. The "true patient" was found.

It should be noted that in other preliminary (as yet unpublished) studies in which the true patient was not a member of the original model set, the MM controller was also able to perform its MM adaptive control function acceptably.

DISCUSSION AND CONCLUSION

The MM dosage designer developed regimens which achieved the therapeutic goals with visibly greater precision than those using traditional single point mean population pharmacokinetic parameter values. Further, the MM controller appear to learn well from the feedback provided by the serum levels, and to control the patient well as it progressed from one feedback cycle (therapy day, or event horizon) to another. The MM program obtains visibly greater precision in achievement of desired therapeutic target goals compared to conventional control based on mean pharmacokinetic parameter values, which is employed today by all maximum aposteriori probability (MAP) Bayesian software in current wide use. A user-friendly clinical version of the MM program is in development.

ACKNOWLEDGMENTS

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REFERENCES


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* Kint was held fixed at 0.002043 hr\(^{-1}\) throughout.
  # all in hr\(^{-1}\)
Figure 1. 3D plot of a Vancomycin population marginal joint density. $V_s =$ slope of volume with respect to body weight. $K_7 =$ slope of $K_e l$ with respect to creatinine clearance. The other parameters $K_{cp}$ and $K_{pc}$, which describe exchange out to and back from the peripheral (nonserum) compartment, are not shown here, but can be similarly displayed, as can any selected pair of parameters.
Figure 2. The 28 Vancomycin population support points listed by the index number (horizontal), and their various probabilities (vertical). The various parameter values associated with each support point are not shown.
Figure 3. Serum concentration trajectories predicted when the regimen to control the mean value of each parameter in the Vancomycin nonparametric population model is given to all many support points which constitute the model. The horizontal dashed line is the 15 ug/ml therapeutic goal. Great diversity in predicted serum concentrations is seen, due to the diversity of patients in the population model.
Figure 4. Serum level trajectories predicted when the MM regimen is given to all support points in the nonparametric population model. The horizontal dashed line is the 15 ug/ml therapeutic goal. Much less diversity in predicted serum concentrations is seen, due to the fact that the MM regimen is specifically designed to achieve the desired goal with the least possible weighted squared error over the course of that day.
Figure 5. Trajectories of the 99% most probable predicted serum level responses during Day 1 of therapy, before feedback. Solid lines: the 95% most probable trajectories. Dotted lines: the next most likely 4%, for the total of 99%. The horizontal dashed line is the 15 ug/ml therapeutic goal.
Figure 6. Serum level response of the "true patient" during therapy day 1 (horizon 1). Horizontal dashed line: the desired goal of 15 ug/ml at 2, 4, 6, 12, 18, and 24 hrs. Solid line: true serum concentrations in the simulated true patient.
Figure 7. Revised model (support point) probabilities following Bayesian feedback from the serum levels during Day 1. They were used to plan the regimen for Day (event horizon) #2.
Figure 8. The 99% most probable serum level trajectories predicted for Day 2 of therapy (event horizon #2). The horizontal dashed line is the 15 ug/ml therapeutic goal.
Figure 9. Serum level responses of the "true patient" during therapy day (event horizon) #2. The horizontal dashed line is the 15 ug/ml therapeutic goal.
Figure 10. Model probabilities updated at the end of therapy day 2, to be used for planning the regimen for day (horizon) #3.
Figure 11. The 99% most probable serum level trajectories predicted for Day 3 of therapy (event horizon #3). The horizontal dashed line is the 15 ug/ml therapeutic goal.
Figure 12. Response of the "true patient" during day (event horizon) #3. The horizontal dashed line is the 15 ug/ml therapeutic goal.
Figure 13. Model probabilities after 3 days of therapy and feedback. The simulated "true patient" (support point #15) was found.