**Subject:** THE PERFORMANCE OF PHARMACOKINETIC PARAMETERS DERIVED FROM A COMPUTER CONTROLLED INFUSION PUMP

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Introduction: Several research groups have used computer controlled infusion pumps (CCIP) to administer intravenous anesthetics according to pharmacokinetic (PK) models. The PK parameters used by the computer model have been derived from conventional PK studies. Conventional PK studies use either a bolus or brief zero-order infusion of drug, followed by a blood sampling scheme designed to characterize the distribution and elimination PK parameters. By contrast, computer controlled infusions use an exponentially declining infusion rate to maintain a constant plasma drug concentration. We investigated whether it was possible to derive reasonable parameters from a PK study using a CCIP, and whether these parameters would improve ability of a CCIP to predict the plasma drug concentration.

Methods: After institutional review board approval and informed consent, we studied 21 patients, ASA status 1 to 4, undergoing a variety of procedures under general anesthesia. Seven of the patients were men. The mean age was 58 (± 11 SD) years. The mean weight was 69 (± 17 SD) kilograms.

The CCIP administered fentanyl to the patients as a bolus followed by an exponentially declining infusion (approximated with 15 second rate changes) to maintain the fentanyl concentration at the desired target. The anesthesiologist titrated the target concentration according to patient response and anesthetic requirements. The patients were divided into two groups. In the first group, the computer used the fentanyl PK parameters of McClain and Hug[1] to control the infusion (11 patients). In the second group, the PK parameters of Scott and Stanski[2] were used (10 patients).

Blood samples were collected at 1 minute intervals for 10 minutes during the initial infusion period, then at increasingly longer intervals, for an average of 372 minutes per patient (range 80 to 1097 min). After changes in target concentration, samples were drawn every minute for several minutes. We collected 603 blood samples, an average of 29 samples per patient. The serum was frozen until the fentanyl was assayed by RIA. The lower limit of detection was 0.25 ng/ml.

PK analysis was done using MKMODEL,[2] an extended least squares non-linear regression program, which we modified to accept the complex fentanyl infusion scheme used by the CCIP. Each patient was fit to a three compartment model to assess the contribution of assay error and model misspecification to the observed variability. MKMODEL was further modified to compute a single three compartment fit on the pooled blood levels from all 21 patients. The PK model was modified to investigate three methods of adjusting the volume of the central compartment ($V_1$) for patient's weight: Model 1: $V_1$ = constant [i.e. no adjustment for weight], Model 2: $V_1$ = scaler * weight, Model 3: $V_1$ = constant + scaler * weight.

We compared the parameters derived from our pooled data with several published parameter sets. We calculated log likelihood (the MKMODEL objective function), percent error (average [absolute error / measured level]) and bias (average [error / measured level]) of our measured blood levels as a function of the predictions from McClain and Hugs parameters, Stanski and Scott's parameters, and the parameters derived directly from the pooled data. The percent error estimates the quality of the fit (0% = perfect fit), while the bias estimates systematic under or over prediction.

Results: The patients were described by their individual three compartment PK parameters with a percent error of 14% (range 6% to 24%), which is consistent with the known assay variability and model misspecification of fentanyl. Table 1 shows the parameters, percent error, bias, and log likelihood for the PK parameters from McClain and Hug, Scott and Stanski, and the three models for $V_1$ we used to fit these 21 patients. The best prediction, in terms of percent error, was when $V_1$ modeled as a scaler times weight (model 2). The best fit, in terms of log likelihood, was when V1 was a constant plus a scaler times weight (model 3).

Discussion: When patients are individually fit to a three compartment model, the PK parameters are, by definition, the best parameters for that patient. The percent error is then a measure of the variability that cannot be eliminated by the optimum parameters. The 14% error of these patients when described by their individual PK parameters suggests that no three compartment PK parameter set will allow a CCIP to infuse fentanyl with less than 14% error. The percent error of 45% for McClain and Hug's PK parameters, and 37% for Scott and Stanski's PK parameters, suggests that in our patients the variability between the population mean parameters and individual patient's parameters accounts for roughly two-thirds of the total percent error. PK analysis of the pooled data generated a parameter set optimized, in terms of log likelihood, for our study population. This parameter set had a percent error of 42%, suggesting no improvement in describing the fentanyl plasma concentrations in these patients.

Although PK analysis of our patients failed to improve the predictive performance of the parameters, it is possible that including specific patient characteristics in the analysis might improve performance. A straightforward and physiologically sensible relationship is to model $V_1$ as a function of weight. The two models investigated yielded fairly small improvements in the percent error when compared with the performance of Scott and Stanski's PK parameters.

We conclude that the predicted plasma fentanyl concentration achievable with a CCIP has an error of 30-40%. Although we have the ability to perform PK analysis on fentanyl when delivered by CCIP, the parameters produced by such analysis do not improve the predictive ability of the pump. Improved performance of these pumps will require use of an intravenous drug with less variability between individual patient's PK parameters and the population mean parameters.

TABLE 1 Published and CCIP fentanyl parameters

| Parameter | McClain | Scott | Model1 | Model2 | Model3 |
|---|---|---|---|---|---|
| $V_1$ constant (liters) | 26.91 | 12.70 | 6.09 | 0 | 2.70 |
| $V_1$ scaler (l/kg) | 0 | 0 | 0 | 0.114 | 0.059 |
| t 1/2 alpha (min) | 1.61 | 1.02 | 0.82 | 0.82 | 0.82 |
| t 1/2 beta (min) | 12.63 | 18.73 | 17.32 | 17.23 | 17.23 |
| t 1/2 gamma (min) | 216.61 | 474.76 | 467.71 | 465.21 | 465.20 |
| K21 | 0.103 | 0.096 | 0.102 | 0.102 | 0.102 |
| K31 | 0.020 | 0.008 | 0.006 | 0.006 | 0.006 |
| Percent error | 45 | 37 | 42 | 32 | 34 |
| Bias (percent) | -31 | -14 | 29 | 1 | 15 |
| Log likelihood | -1588 | -1358 | -1183 | -1202 | -1122 |

1. McClain, D.A., Hug C.C.: Clin Pharm Ther 28:106-114, 1980
2. Scott, J.C., Stanski, D.R.: J. Pharm Exp Ther 240:159, 1987
3. Holford, N: MKMODEL Users Manual, Elsevier, 1986