Derivation and Cross-validation of Pharmacokinetic Parameters for Computer-controlled Infusion of Lidocaine in Pain Therapy

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Background: Lidocaine administered intravenously is efficacious in treating neuropathic pain at doses that do not cause sedation or other side effects. Using a computer-controlled infusion pump (CCIP), it is possible to maintain the plasma lidocaine concentration to allow drug equilibration between the plasma and the site of drug effect. Pharmacokinetic parameters were derived for CCIP administration of lidocaine in patients with chronic pain.

Methods: Thirteen patients (mean age 45 yr, mean weight 66 kg) were studied. Eight subjects received a computer-controlled infusion, targeting four increasing lidocaine concentrations (1–7 $\mu g \cdot ml^{-1}$) for 30 min each, based on published kinetic parameters in which venous samples were obtained infrequently after bolus administration. From the observations in these eight patients, new lidocaine pharmacokinetic parameters were estimated. These were prospectively tested in five additional patients. From the complete data set (13 patients), final structural parameters were estimated using a pooled analysis approach. The interindividual variability was determined with a mixed-effects model, with the structural model parameters fixed at the values obtained from the pooled analysis. Internal cross-validation was used to estimate the residual error in the final pharmacokinetic model.

Results: The lidocaine administration based on the published parameters consistently produced higher concentrations than desired, resulting in acute lidocaine toxicity in most of the first eight patients. The highest measured plasma concentration was 15.3 $\mu g \cdot ml^{-1}$. The pharmacokinetic parameters estimated from these eight patients differed from the initial estimates and included a central volume one-sixth of the initial estimate. In the subsequent prospective test in five subjects, the new parameters resulted in concentrations evenly distributed around the target concentration. None of the second group of subjects had evidence of acute lidocaine toxicity. The final parameters ($\pm$ population variability expressed as %CV) were estimated as follows: V_1 0.101 $\pm$ 53% $l \cdot kg^{-1}$, V_2 0.452 $\pm$ 33% $l \cdot kg^{-1}$, Cl_1 0.0215 $\pm$ 25% $l \cdot kg^{-1} \cdot min^{-1}$, and Cl_2 0.0589 $\pm$ 35% $l \cdot kg^{-1} \cdot min^{-1}$. The median error measured by internal cross-validation was +1.9%, and the median absolute error was 14%.

Conclusions: Pharmacokinetic parameters for lidocaine were derived and administration was prospectively tested *via* computer-controlled infusion pumps for patients with chronic neuropathic pain. The estimated parameters performed well when tested prospectively. A second estimation step further refined the parameters and improved performance, as measured using internal cross-validation. (Key words: Anesthetics, local: lidocaine. Pain: neuropathic. Pharmacokinetics: computer-controlled infusion pump. Statistical methodology, mixed-effects model: cross-validation.)

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LIDOCAINE administered intravenously is efficacious in treating neuropathic pain[1] at doses that do not cause sedation or other side effects. The utility of treating chronic pain states with intravenous anesthetics can be tested easily with lidocaine because of its short duration of action. If treatment with intravenous lidocaine produces relief from neuropathic pain, long-term treatment with an oral sodium channel blocker, such as mexiletine, may be efficacious.

Intravenous bolus administration easily can be associated with severe side effects because of lidocaine's narrow therapeutic range and potential for central nervous system toxicity. For testing pain relief, the lidocaine plasma concentration must remain within the therapeutic range long enough to allow the plasma concentration to equilibrate with the sites of drug effect at the spinal or supraspinal level[2] and at injured pe-

ripheral nerves.[3] Using a computer-controlled infusion pump (CCIP) it is possible to produce stable and predictable concentrations of intravenously administered drugs. CCIP administration results in more stable concentrations than observed with either bolus injection or constant-rate infusion because the CCIP approach compensates for drug distribution into peripheral tissues.

A CCIP approach is only accurate if the pump is programmed with pharmacokinetic parameters that are appropriate for the population being treated and, possibly, for the method of drug delivery. Gustafsson *et al.* observed that parameters derived from a CCIP study are better suited for use in a CCIP than parameters derived from a standard pharmacokinetic study wherein the drug was given by a brief infusion.[4] The goal of this study was to derive pharmacokinetic parameters suitable for CCIP administration of lidocaine to patients with neuropathic pain and to prospectively validate the derived model.

Methods

Clinical Methodology

With Institutional Review Board approval, 13 consenting patients at the Stanford Pain Clinic were enrolled in the study during a 3-yr period. All patients had pain of possibly neuropathic origin. The patient demographics were as follows: Mean age was 45 yr, ranging between 31 and 62. Nine women and four men participated in the study. The mean weight was 66 kg, ranging from 49 to 114 kg.

The patients were studied in the procedure room at the Stanford Pain Clinic. An 18-G catheter was placed in a forearm vein for lidocaine administration, and a 20-G catheter was placed in a radial artery at the wrist for blood sampling and blood pressure monitoring. Patients were monitored with an electrocardiogram and a pulse oximeter.

The lidocaine 2% infusion was controlled by a CCIP.† Four plasma concentrations were targeted: 1, 3, 5, and 7 $\mu g \cdot ml^{-1}$. Each concentration was maintained for

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† The software, STANPUMP, is available at no charge from the author (S.L.S.). STANPUMP is written in C and runs on any 8088-compatible MS-DOS computer with a serial port. STANPUMP currently supports the Harvard Pump 22 and the Graesby 3400. STANPUMP can be obtained from the World Wide Web at URL: http://pkpd.icon.palo-alto.med.va.gov.

precisely 30 min. The 30-min duration of each target concentration provided time to adequately assess whether there was an analgesic response to the lidocaine. Patients frequently were asked about central nervous system side effects of lidocaine, such as perioral numbness or light-headedness. If side effects were observed or reported by the patient, the infusion was stopped.

Blood Sampling and Assay

Blood samples for analysis of lidocaine plasma concentration were obtained before the infusion and at 2, 4, 6, 8, 10, 20, and 30 min during each of the four 30-min infusion periods. No concentration data were gathered during washout. Plasma lidocaine concentrations were measured using gas chromatography with a nitrogen-phosphorus detector with a quantitation limit of 0.05 $\mu g \cdot ml^{-1}$. Extractions of 0.2 μg lidocaine from variable serum volumes (0.02, 0.05, 0.1, and 0.5 ml) resulted in a coefficient of variation of 1.7%. The lidocaine assays were performed within 2 h after the blood sample was taken.

Pharmacokinetic Analysis: Overview

Pharmacokinetic parameters published by Rowland *et al.*[5] were programmed into the CCIP. The parameters were obtained from the published individual parameters by averaging the parameters from the 50- and 100-mg bolus sessions and the intravenous infusion session. In the following sections, we refer to the parameters from Rowland as parameter set A. The performance of parameter set A was tested prospectively in eight subjects. The measures of performance are defined below.

The observations from the first eight subjects were used to estimate another set of lidocaine pharmacokinetic parameters (parameter set B).[6] The details of the estimation are provided below. These new parameters were programmed into the CCIP and prospectively tested in another five patients in a protocol otherwise identical to that used for the first eight patients.

After the prospective test of parameter set B, we combined the observations from all 13 subjects and estimated a new parameter set for lidocaine administration by CCIP (parameter set C) as described below. Parameter set C was estimated to include data from as large a sample as possible in the final parameter set. The performance of parameter set C was tested using internal cross-validation[7] in lieu of a prospective trial.

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Pharmacokinetic Analysis: Modeling

Parameter sets B and C were estimated using the regression program NONMEM with a user-supplied PRED routine that set parameters for two- and three-compartment mamillary models in terms of volumes and clearances. Model selection between two and three compartment models, and the choice of demographic covariates (age, weight, gender) was made using the log likelihood as previously described.[8] Covariates were tested using a linear model in which pharmacokinetic parameters (all volume and clearance terms) were expressed as covariate times a slope factor plus an intercept:

$$P = \theta_1 \cdot \text{covariate} + \theta_2,$$

where P is a volume or clearance value, θ_1 and θ_2 are the parameters to be estimated, and the covariate is weight, age, or gender. This model was refined and parameters were deleted from the model according to the criterion given by Mandema *et al.*[9] A proportional residual error model was assumed in the nonlinear regression procedure. All volumes and clearances were assumed to be logarithmically distributed.

Once the structure of the model was defined (*e.g.*, two *vs.* three compartments, parameters (if any) influenced by covariates), the final parameter estimates were obtained as follows:

1. The interindividual variability on the volumes and clearances was fixed at 0.
2. The structural estimates were obtained (naive pooled-data approach). The naive pooled-data approach has been shown to provide model estimates that accurately predict concentrations with computer-controlled drug infusions.[4,10] A second reason to use a naive pooled-data approach was that it can help avoid the problems with model misspecification occasionally seen with mixed-effect models,[8,11] (although the current data set did not show evidence of model misspecification with the mixed-effect approach).
3. Fixing the structural parameters at the values estimated in the above step, the interindividual variance was estimated on each volume and clearance term, assuming a logarithmic distribution. Estimates of the distribution of the parameters are potentially useful for Bayesian updating, for stochastic control, and to understand the sources of variability within the population.[12]

Pharmacokinetic Analysis: Cross-Validation

The residual errors from a regression analysis underestimate the errors expected from prospective use of the model. Cross-validation provides a nearly unbiased estimate of the ability of the model to predict the observations. The leave-one-out approach to cross-validation is performed as follows:

1. If there are *n* individuals in the sample, *n* different structural parameter sets are estimated. Each of the *n* parameter sets is estimated from *n* − 1 individuals (in other words, an individual is left out for each model).
2. The structural parameters are used to predict the observations in the excluded individual. Because this individual's observations did not contribute to the parameter estimates, the ability of the model to predict this individual's observations is not favorably biased. This step is repeated for the *n* individuals, producing *n* approximately unbiased measures of performance.
3. Two composite measures of the *n* unbiased measures of performance were calculated, the median cross-validation prediction error (MDCV) and the median absolute cross-validation prediction error (MDACV), as defined below.

As mentioned, cross-validation is nearly unbiased. The cross-validated performance probably is slightly biased against the model being validated. This is because the model being validated is derived from *n* individuals, whereas the submodels used to validate it are derived from *n* − 1 individuals. Thus, it would be expected that the submodels are slightly less accurate at prediction than the model being validated.

Two cross-validations were performed: parameter set B, using the 8 individuals who contributed data to parameter set B, and parameter set C, using the 13 individuals who contributed to parameter set C.

Pharmacokinetic Analysis: Measurement of Prediction

Three types of prediction error can be measured: performance errors (PE), weighted residuals (WR), and cross-validation prediction errors (CV).

Prediction errors (PRE) are calculated as the error, weighted by the predicted concentration[13]:

$$\%\text{PRE} = \frac{C_o - C_p}{C_p} \cdot 100,$$

where C_o is the observed concentration, and C_p is the predicted concentration.

The formulas for %PE, %WR, and %CV look identical but differ in how the C_p is obtained.

Performance errors are the differences between the observed concentrations and those predicted by the computer-controlled infusion pump in prospective tests. They are calculated as the error, weighted by the predicted concentration. C_p is the concentration predicted by the CCIP.

The weighted residuals are the differences between the observed concentrations and the predictions of the final model derived from those concentrations, weighted by the predicted concentrations. They are a retrospective measurement of prediction. C_p is the concentration predicted by estimated pharmacokinetic parameters.

The cross-validation prediction errors are the differences between the observations in each individual and the prediction of a model calculated from the subsample from which that individual has been excluded. It is a nearly unbiased estimate of the prediction error that would be expected under identical experimental conditions.[14] C_p is the concentration predicted by model estimated in all individuals except the individual from whom the observations are derived.

From the initial eight subjects who received lidocaine according to the pharmacokinetics of Rowland *et al.*, we calculated the median performance error (MDPE) and the median absolute performance error (MDAPE) in a subject-specific calculation as follows[13]:

$$MDPE = median(PE_1, PE_2, \cdots, PE_n),$$

$$MADPE = median(|PE_1|, |PE_2|, \cdots, |PE_n|),$$

where n is the total number of observations, PE_i the prediction error of the ith observation, and $\overline{PE_i}$ the absolute prediction error of the ith observation.

We also calculated the MDPE and MDAPE for the second group of five subjects who received lidocaine using parameter set B. We calculated the median weighted residual (MDWR), the median absolute weighted residual (MDAWR), the median cross-validation prediction error (MDCV), and the median absolute cross-validation prediction error (MDACV) in an identical manner to the MDPE and the MDAPE.

For parameter set B, these performance measures were calculated from the first eight individuals. For parameter set C, these performance measures were calculated from the entire population of 13 individuals.

We compared the cross-validation measures of performance for parameter set B to the prospective measures of performance obtained for parameter set B to investigate the ability of the cross-validation to predict prospective performance.

The measures of prediction error were graphed over time to provide a visual assessment of error.

Results

Clinical Assessment

Only two of the first eight subjects (parameter set A) tolerated the infusion over the whole planned range. All of the subjects reported transient symptoms of lidocaine toxicity after the step changes, even in lower target concentrations. The symptoms included perioral dysesthesia, light-headedness, and myoclonus. There were no seizures. The highest measured concentration was 15.3 µg/ml, which occurred 2 min after a step-change in target concentration. In two subjects, the infusion was stopped prematurely for side effects that were not related to concentration. One subject became anxious after the second target, and one subject experienced chest pain after the second target. In both cases, the concentrations were unremarkable compared to those in subjects who continued with the study.

In the second group of five subjects (parameter set B), none reported side effects, but one patient felt uncomfortable with the study situation, and the infusion was stopped. In this patient, the initial target concentration was erroneously set to 5 $\mu g \cdot ml^{-1}$ instead of 1 $\mu g \cdot ml^{-1}$.

Pharmacokinetic Analysis

A total of 291 blood concentration measurements were taken from the 13 individuals. No samples were excluded from the analyses. The number of samples per subject ranged from 11 (in the two subjects in which the infusion was stopped) to 28.

Table 1 shows parameter sets A, B, and C. A representative individual from the first eight subjects is shown in figure 1. The measured lidocaine concentration is consistently above the target concentration, particularly after each increase in target concentration. Figure 2 shows the performance errors over time for the first eight subjects. In seven of eight subjects, the measured lidocaine concentrations were consistently greater than the target concentrations; and in all subjects, there was an overshoot immediately after the
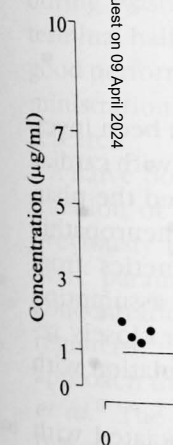
Table 1. Pharmacokinetic Parameters for Lidocaine

	Parameter Set A	Parameter Set B	Parameter Set C		
			Typical Value	SE	CV (%)
Central volume	34.51	$0.088 \text{ L} \cdot \text{kg}^{-1}$	$0.101 \text{ L} \cdot \text{kg}^{-1}$	0.0162	53.4
Peripheral volume	60.61	$0.4 \text{ L} \cdot \text{kg}^{-1}$	$0.452 \text{ L} \cdot \text{kg}^{-1}$	0.058	33.0
Clearance 1	$0.87 \text{ L} \cdot \text{min}^{-1}$	$0.02 \text{ L} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	$0.0215 \text{ L} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	0.00148	24.5
Clearance 2	$2.0 \text{ L} \cdot \text{min}^{-1}$	$0.056 \text{ L} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	$0.0589 \text{ L} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	0.00581	35.4
k_{10}	0.0253 min^{-1}	0.227 min^{-1}	0.213 min^{-1}		
k_{12}	0.0576 min^{-1}	0.636 min^{-1}	0.583 min^{-1}		
k_{21}	0.0328 min^{-1}	0.14 min^{-1}	0.130 min^{-1}		
Weighted residuals (retrospective) (%)					
MDWR		0.7 (first 8)	1.7 (13)		
MDAWR		10 (first 8)	13 (13)		
Cross-validation prediction errors (%)					
MDCV		1.1 (first 8)	1.9 (13)		
MDACV		12 (first 8)	14 (13)		
Performance errors (prospective) (%)					
MDPE	31 (first 8)	−6 (last 5)			
MDAPE	33 (first 8)	15 (last 5)			

SE = standard error of parameter estimate; CV = coefficient of variation (population variability); MDWR = median weighted residuals; MDAWR = median absolute weighted residuals; MDCV = median cross-validation prediction error; MDACV = median absolute cross-validation prediction error; MDPE = median performance error; MDAPE = median absolute performance error.

Values in parentheses are number of patients.

change in target concentration. This explains the transient toxicity observed in all subjects immediately after each change in target concentration. The MDPE in the first eight subjects was +31%, and the MDAPE was 33%.

Pharmacokinetic analysis of the data from the first eight subjects generated a two-compartment model.

Weight proved to be a significant covariate on all volumes and clearances. No other patient covariate improved the model. The pharmacokinetic parameters estimated from the first eight subjects are shown in table 1 (parameter set B). V_1 was fivefold smaller in parameter set B, as suggested by the large overshoots observed in the prospective trial of parameter set A. The MDWR and MDAWR of parameter set B, as applied

Fig. 1. Time course of measured lidocaine concentrations (dots) and of the predicted lidocaine concentrations (solid line) with parameter set A in a typical patient from the first part of the study. Note the high plasma concentration after each change in the target concentration.
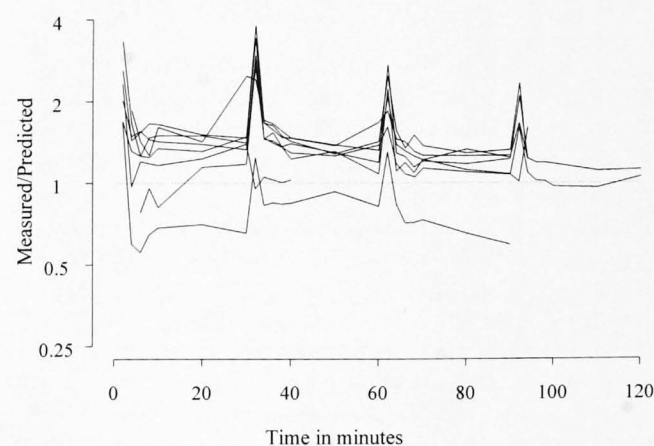
Fig. 2. The computer-controlled infusion pump performance errors over time for each of the first eight patients dosed according to parameter set A.

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to the first eight subjects, were +0.7% and 10%, respectively. In the cross-validation, the MDCV and MDACV of parameter set B were +1.1% and 12%, respectively, showing the expected decrement in prediction with the cross-validation step.

Figure 3 is representative of the performance prospectively obtained with computer-controlled infusion of lidocaine using parameter set B. The measured concentrations were close to the target, and the initial overshoot was no longer observed. The performance errors over time prospectively obtained in all five patients receiving lidocaine using parameter set B are shown in figure 4. The MDPE was −6.0%, and the MDAPE was 15%. Also shown in figure 4 are the cross-validation prediction errors for parameter set B in the first eight patients (dashed lines). The dashed lines predicted errors of similar magnitude to the performance errors prospectively observed. Although the prospective test indicated more bias than the cross-validation (MDPE of −6% *vs.* an MDCV of +1.1%), the absolute inaccuracy was similar (MDAPE of 15% *vs.* MDACV of 12%).

The pharmacokinetic parameters estimated from all 13 individuals are shown in table 1 (parameter set C). Although the parameters were calculated using a naive pooled-data approach,[8,11] the standard errors of the parameters and interindividual variability about these parameters were subsequently estimated using NONMEM. The standard errors and interindividual variability are shown in table 1. The standard errors of the estimates were small compared to the estimates themselves. This
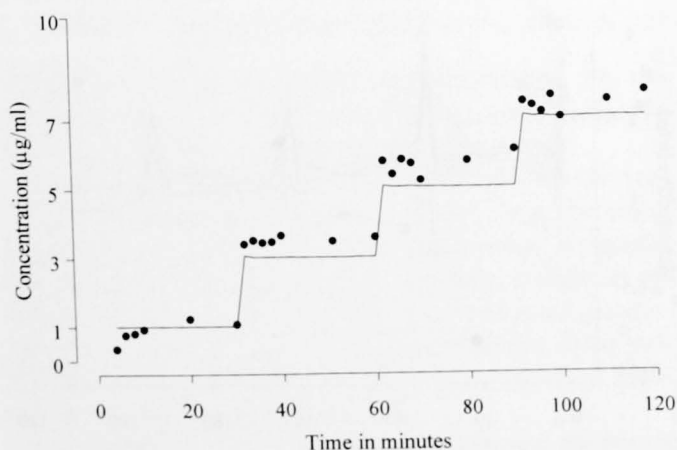
Fig. 4. The predicted performance over time for parameter set B calculated by cross-validation (dashed lines) and calculated from the prospective test (solid line).

suggested the volumes and clearances estimated using the naive pooled-data approach were similar to those that would have been estimated using a mixed-effects analysis. The interindividual variability of 24.5–53.4% (CV) is similar to that observed for many intravenous anesthetics.[8,11]

Prospectively, the MDWR and MDAWR for parameter set C were +1.7% and 13%, respectively. The MDCV and MDACV were +1.9% and 14%, respectively, again reflecting the expected decrement in predictive accuracy in the cross-validation. Figure 5 shows the prediction errors from the cross-validation of parameter set C in all 13 subjects.

Discussion

The pharmacokinetics of lidocaine have been investigated in normal subjects[5] and in subjects with cardiac failure.[15] No studies to date have examined the pharmacokinetics of lidocaine in patients with neuropathic pain. We programmed the pharmacokinetics from healthy volunteers into the CCIP on the assumption that patients with neuropathic pain more closely resembled a healthy population than a population with heart failure.

The first eight study sessions were associated with clinical evidence of drug overdose, which was confirmed by the lidocaine concentration measurements. Although the lidocaine plasma concentrations were high, there were no adverse outcomes. Subsequent pharmacokinetic analysis demonstrated that the central
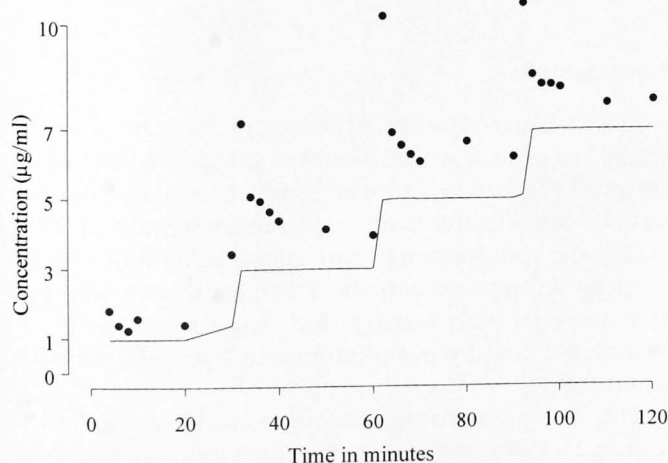

Fig. 3. Time course of measured lidocaine concentrations (dots) and of the predicted lidocaine concentrations (solid line) with parameter set B in a typical patient from the second part of the study.

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volume in ou... approximately... explained by... current study... the current stu... the study by I... with the initia... These differe... smaller estim... study by Row... rived pharma... ical evidence... targeting by t... during wash... terminal half... good perform... ministration... research.

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Fig. 5. The predicted performance errors over time for each of the 13 patients based on the cross-validation analysis.

volume in our patients, given this study design, was approximately fivefold smaller. The difference can be explained by differences in study design between the current study and that of Rowland *et al.* In particular, the current study used rapid arterial sampling, whereas the study by Rowland *et al.* gathered venous samples, with the initial sample 2–3 min after a bolus injection. These differences would be expected to produce a smaller estimate of V_1 in the current study than in the study by Rowland *et al.* Prospective testing of the derived pharmacokinetic parameters resulted in no clinical evidence of acute lidocaine toxicity and in accurate targeting by the CCIP. Because we did not gather data during washout, it is likely that our estimate of the terminal half-life is not accurate. We would not expect good performance with prospective testing of drug administration by CCIP lasting longer than in the current research.

A naive pooled analysis approach was chosen for estimation of the parameter sets B and C. We showed previously that this approach estimates pharmacokinetic parameters that accurately predict the plasma concentrations when prospectively tested for infusion regimens.[4,10,16] The relative merits of the pooled-data approach to other approaches are discussed by Kataria *et al.*[8] The naive pooled-data approach can produce biased estimates when data are systematically imbalanced. Although two subjects were withdrawn from this study prematurely, there was no indication that their concentrations were systematically different from those observed in other individuals who continued in the study. Thus, the withdrawal of these individuals

does not introduce systematic imbalance into the study design.

An important drawback of the naive pooled modeling approach is that it does not estimate the interindividual variability in the parameters. The knowledge of this variability is important for several reasons. For a drug with a narrow therapeutic window and serious side effects, dosage regimens should be developed by calculating confidence bounds for the expected plasma concentration after a certain dose. These confidence bounds are best calculated incorporating the interindividual variability. Another use for interindividual variability is that, in some cases, it is possible to obtain plasma concentration data during the infusion. This is so for lidocaine because most hospitals have lidocaine assays available for clinical use. With *a priori* knowledge of the distribution of pharmacokinetic parameters within a population, it is possible to apply Bayesian updating during the course of drug therapy to update the pharmacokinetic parameters used to program the pump. This has been specifically incorporated into the STANPUMP program, although it was not used in the current trial.

We have described a method for calculating the variance on the kinetic parameters using a mixed-effects model with the structural model parameters fixed at pooled estimates. This method will result in biased variance estimates in that we penalize the variance-covariance matrix by possibly imprecise mean population parameters, although we gain the precision and the robustness of the parameters obtained from the pooled approach. There is no statistical reason to prefer pooled or mixed-effects analysis, and our approach represents a novel compromise between the two approaches.

When characterizing a drug's kinetics, it is important to validate the new parameters. Traditionally this is done in a prospective study. In some cases, recruitment of new patients may be time-consuming. For example, recruitment of 13 patients in the current study required 3 yr. Moreover, high-resolution pharmacokinetic studies are expensive. If we choose to withhold data from the observations used to estimate the final parameters, we decrease the accuracy of the parameter estimates. Balanced against the cost and time associated with prospective trials is the need to provide an estimate of the likely prospective performance under identical experimental conditions. Because the weighted residuals are favorably biased as estimates of prospective performance and pro-

spective measures are very expensive in time and money, we proposed cross-validation as a useful measure of the expected prospective performance.[7] In this study, the cross-validation of parameter sets B and C showed a small decrement in predictive accuracy compared with the weighted residuals. This is expected, because the cross-validation should remove the favorable bias in the weighted residuals. For parameter set B, the magnitude and time course of the prediction errors calculated using cross-validation in the first eight subjects was in good agreement with the magnitude and time course of the prospectively measured performance errors in the subsequent five subjects (fig. 5). This supports the use of cross-validation as an efficient means of estimating the expected prospective performance.

Prospective studies and cross-validation are both techniques to estimate the likely performance of a model under experimental conditions identical to those in the study. Both of them would be expected to predict the performance less accurately for studies in which the experimental conditions were changed. Thus, cross-validation and truly prospective studies share a lack of applicability to experimental conditions beyond those of the reference studies. For example, if the population in a prospective study differed from the population in the current study in some significant manner, it is likely that the performance of our lidocaine pharmacokinetic parameters would be worse than measured in our cross-validation analysis. Additionally, if the pharmacokinetics of a drug are influenced by dose (*i.e.*, the pharmacokinetics are nonlinear), the performance of the pharmacokinetics in a prospective trial is likely to be worse than estimated using cross-validation.

In conclusion, we have derived pharmacokinetic parameters suitable for computer-controlled infusion of lidocaine in chronic pain patients. A novel estimation approach was used that combined a naive pooled-data approach for estimation of the structural model with a mixed-effects approach for estimation of the interindividual variability. Cross-validation was used to test the estimated parameters, and (for parameter set B) the results of the cross-validation were compared with truly prospective measures of performance. Theoretically, cross-validation offers an efficient and statistically sound approach for testing the performance of newly derived parameters. Our results support the theoretical benefits of cross-validation. The final model for lidocaine should be ap-

propriate for computerized administration to patients with neuropathic pain.

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