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A POPULATION PHARMACOKINETIC MODEL OF EPIDURAL LIDOCAINE IN GERIATRIC PATIENTS: EFFECTS OF LOW-DOSE DOPAMINE

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Abstract

Purpose—To develop a population pharmacokinetic (PK) model of epidural lidocaine in geriatric patients, to search for any difference in the PK behavior of epidural lidocaine when dopamine is given concurrently, and to develop a descriptive PK model from which to calculate dosage and infusion regimens of epidural lidocaine to define and achieve desired target goals in either the epidural or the serum compartment.

Methods—Twenty patients over age 65, undergoing peripheral vascular surgery using continuous epidural lidocaine anesthesia, were studied. Ten patients also received an intravenous (IV) infusion of placebo (normal saline), while ten other patients received an IV infusion of dopamine at 2 µg/kg/min. Total plasma lidocaine concentrations (gas-chromatographic assay) were measured from arterial samples just before injecting the first epidural dose (baseline) and then at 5, 15, 30, 60, 90, 120 min and hourly thereafter. Samples were also taken when the lidocaine infusion was stopped at the end of the surgery, and at 30min, 60min, 90min, 2h, 3h, 4h, and 5h after surgery. The nonparametric adaptive grid (BigNPAG) computer program in the MM-USCPACK collection was utilized for population PK modeling to obtain the entire discrete maximum likelihood joint parameter distribution. The assay error polynomial was determined to be $0.2 + 0.05 \cdot C$. The structural population PK model was linear, and had 3 compartments, each with first order transfer kinetics.

Results—Lidocaine had a very fast transfer rate constant ($K_{a\text{ part}} + K_{20}$) from the epidural space to the serum compartment. This rate was slowed, by over 41%, by dopamine. The mean rate constant of elimination from the serum compartment (K_{20}) was increased by 9.7 % by dopamine. The mean rate constant for drug movement from central to peripheral compartment (K_{23}) was increased by 47% in the dopamine patients. The mean rate constant back from the peripheral to the central compartment (K_{32}) was slowed by 46% by dopamine. There was no obvious difference in the apparent volume of distribution of the central compartment between the placebo and the dopamine patients. In this model, there was no specific compartment for Lidocaine in the cerebrospinal fluid (CSF). CSF is probably one of the components of the overall peripheral, nonserum, compartment in our model.

Conclusions—In this first population model of epidural lidocaine using a statistically consistent method, low-dose dopamine appears to decrease the rate of transfer of lidocaine from the epidural to the serum compartment, and to increase both the rate of elimination of lidocaine as well as its transfer between the central (serum) and peripheral compartment, presumably by increasing tissue perfusion. Serum lidocaine concentrations were slightly less in the dopamine patients. Dosage requirements (overall hourly weight-adjusted infusion rates) were slightly less for the dopamine patients, consistent with the slower removal of lidocaine from the epidural compartment. This model should be useful to design more optimal and individualized epidural lidocaine infusion regimens to define and achieve desired target goals in the epidural or the serum compartment.

INTRODUCTION

Continuous epidural anesthesia has been widely adopted as an anesthetic technique for patients undergoing peripheral vascular surgery (1). Epidural anesthesia is desirable in elderly patients because it attenuates the stress response to surgery, reduces the incidence of deep vein thrombosis, increases vascular graft blood flow, and reduces the incidence of reoperation for inadequate tissue perfusion when compared to general anesthesia (2,3). Peripheral vascular surgery may be lengthy, and rather large amounts of local anesthetic may be required during its course by continuous epidural infusion or by intermittent boluses. Despite the fact that lidocaine undergoes extensive elimination by hepatic first-pass metabolism (4), prolonged administration may result in near-toxic serum concentrations (5). This may be especially true for elderly patients with diminished cardiac function, because any condition that decreases cardiac output, such as heart failure or treatment with β -adrenergic blockers (6), reduces lidocaine delivery to the liver and may result in accumulation of lidocaine in the central (serum concentration) compartment (7). Finally, epidural anesthesia, with its effects on autonomic innervation, can itself cause a decrease in hepatic blood flow (8). On the other hand, any condition or intervention that selectively increases hepatic blood flow, such as an infusion of low-dose dopamine, may also increase delivery of lidocaine to the liver and thus reduce serum lidocaine concentrations (8,9).

In a recent study we tested this hypothesis, but did not confirm it (5). We found that the serum lidocaine concentrations during epidural infusion reach high levels in both groups, with quite comparable mean maximum concentrations (5.8 and 5.7 $\mu\text{g/mL}$, in the placebo and dopamine groups, respectively). However, the mean hourly lidocaine requirements during surgery appeared to be somewhat higher in patients receiving low-dose dopamine (290 vs. 267 mg/h) which resulted in apparently higher total lidocaine administration in the dopamine patients at hour 4 of surgery (5). This might be expected to result in higher serum lidocaine concentrations, but this was not found (5). Therefore, it appears that dopamine did, to some degree, reduce serum lidocaine concentrations. It is interesting that informational material for Xylocaine describes slowed absorption and reduction of serum concentrations by the addition of epinephrine (10). Those results prompted us to reexamine and reanalyze that data. The present manuscript now describes a rigorous population pharmacokinetic model based on that previous data (5), and reveals a different appraisal of the dosage requirements in the presence of dopamine.

The pharmacokinetics of intravenously administered lidocaine have been previously described by a two-compartment model with a central (serum) compartment, the site of its antiarrhythmic action and its elimination, and a peripheral (nonserum) compartment of fluid and/or tissues into which distribution of the drug occurs from the central compartment (11). In the present analysis we added an epidural space compartment, the site where the administration of lidocaine takes place during epidural anesthesia, to this basic model. We therefore used a three-compartment linear model to examine the population pharmacokinetics of epidural lidocaine,

as well as the effects of dopamine upon lidocaine pharmacokinetics, in this geriatric patient population.

MATERIALS AND METHODS

Twenty patients over age 65 were scheduled for peripheral vascular surgery at the Cleveland Clinic, Cleveland Ohio, using epidural anesthesia (5). With that center's Institutional Review Board approval and informed consent signed, we included in this study only patients with normal cardiac function (preoperative echocardiogram), and normal hepatic and renal function for age (normal serum transaminases and serum creatinines). None of our patients were taking β -adrenergic blockers. Ten patients were randomly assigned to receive an IV infusion of dopamine at 2 $\mu\text{g}/\text{kg}/\text{min}$ (dopamine group), and 10 to receive an IV infusion of placebo (normal saline) at the same volume rate as the dopamine. These infusions ran continuously until they were stopped at the end of surgery (final closure of incision).

Five minutes after the beginning of either the dopamine or placebo infusion, a bolus of 20 mL of 2% lidocaine (400 mg) was injected through an epidural catheter that had been inserted 3 cm into the epidural space at the L₂₋₃ interspace. Exactly thirty minutes later, an epidural infusion of 2% lidocaine was begun at 10 mL/h (200 mg/hr), until the end of surgery. Five mL of 2% lidocaine (100 mg) boluses were used as needed to supplement the epidural infusion for inadequate surgical analgesia. If the anesthetic level rose above the T₈ dermatome, the epidural infusion was decreased to 5 mL/h (100 mg/hr) until the level returned to the T₈ dermatome or below. Analgesic levels were tested with pinprick throughout the surgery. Phenylephrine, in 100 μg doses, was used if the systolic blood pressure was less than 90 mmHg.

Arterial blood samples were assayed for total serum lidocaine concentrations by the gas-liquid chromatographic assay in routine use at that center. Arterial sampling was chosen as all patients had an arterial line placed, and none had a central line placed. It was felt to be inappropriate to do multiple venipunctures when all patients had an easily accessible arterial line to use for sampling. The samples were all obtained at least 5 minutes after any change in an infusion regimen, so that several circulation times had elapsed before any sampling was done after such a change, and any rapid differences between arterial and venous samples would not be perceived.

Samples were taken just before injecting the first epidural dose (baseline) and then at 5, 15, 30, 60, 90, 120 min, and hourly thereafter. Another sample was taken when the lidocaine infusion was stopped at the end of surgery. Following the termination of the lidocaine infusion, samples for total serum lidocaine concentration continued to be taken at 30, 60 and 90 minutes and at 2, 3, 4, and 5 hours after termination of lidocaine administration. The lower detection limit for this assay was stated by the hospital laboratory to be 0.02 $\mu\text{g}/\text{mL}$ with the linear range of the method between 0.20 and 20.0 $\mu\text{g}/\text{mL}$, covering the data described in this report. However, the error pattern of the assay, evaluated by us over its working range from the raw data, was best described by the following polynomial equation: $\text{SD} = 0.2 + 0.05C$, where SD = assay standard deviation and C = measured lidocaine concentration, both in $\mu\text{g}/\text{mL}$.

In addition, gamma, a measure of extra environmental noise, was also computed. Gamma was used as a multiplier of the assay error pattern, so that total noise, both assay and environmental, equaled gamma times the assay error polynomial. In this case, the total overall noise SD = $\text{gamma} \times (0.2 + 0.05C)$. If gamma is small, close to 1.0, it suggests that the assay noise is essentially all the noise, and that the environmental noise is small, close to zero. If gamma = 2, it suggests that the assay noise is about half the overall noise, or that the overall noise is about twice that of the assay error polynomial. Gamma often ranges from about 1 to about 4, but may at times be much higher, close to 10, for example, if the environmental noise is great.

The ability to compute gamma is most useful in understanding the relative contributions of the assay noise compared to the other environmental sources of noise. These other sources can be the error with which the doses are prepared and administered, errors in recording the timing of the doses and the serum samples, model misspecification, and changing parameter values during the period of the data collection and analysis.

The data of each patient (age, weight, height, boli and infusions of lidocaine, duration of the lidocaine infusions, and the serum lidocaine concentrations) were entered into patient data files using the PASTRX program in the USCPACK PC clinical software (12).

The Pharmacokinetic Model

Model parameters were selected to overcome the problem of the lack of unique model parameter identifiability which accompanies a structural model having both absorptive and elimination rate constants. This is often called the “flip-flop” problem. It exists because the absorptive, elimination, and volume parameters cannot be uniquely identified. Absorption and elimination parameter values can actually be switched, and a different apparent volume of distribution will be found. Both sets of parameter values provide equally good solutions to the model. However, one can choose to have either the absorption or the elimination parameter be the faster one, and to use that particular solution. We chose to have the absorption parameter be the faster one, as shown in Figure 1.

The Population Pharmacokinetic Analysis

Pharmacokinetic analysis was carried out using the nonparametric adaptive grid (BIGNPAG) population modeling program (13-15) in the MM-USCPACK collection of software, version 0.11. The assay error polynomial (see above) was entered. Gamma, the measure of extra environmental noise, was also computed as described above (13-15). The BIGNPAG program computes the full discrete overall parameter joint density for the 3-compartment model, as well as the marginal probability density functions for each PK parameter. The entire joint distribution of the population PK parameter values which is most likely given the raw population data and the weighting scheme used (assay error and Gamma) is therefore estimated. No assumptions about the shape of the parameter distributions are required. The means, medians, and standard deviations of each PK parameter are also obtained. BIGNPAG can operate, if necessary, using sparse patient data files including only one serum sample per patient (12-15). BIGNPAG is statistically consistent in its behavior (14-15) - that is, the more subjects that are studied in a population, the more closely the results obtained approach the true population results (14-15). Such behavior is not guaranteed by many other population modeling programs in current wide use (15).

Pharmacokinetic Parameter Estimation

Model parameters were defined as (K_a part + K_{20}), the two components of the faster absorptive rate constant for transfer of lidocaine from epidural to central compartment; K_{20} , the slower rate constant for elimination from the central compartment; K_{23} and K_{32} , the rate constants for drug movement from central to peripheral tissue compartment, and back, respectively; and V_2 , the apparent volume of distribution of lidocaine in the central compartment.

Patient data were analyzed in 3 ways:

1. Analyzing only the data of the placebo patients. This analysis computed the population PK parameter values without any influence of dopamine.
2. Analyzing only the data of the dopamine patients. This analysis evaluated the influence of dopamine on the PK parameter values in the population.

3. Analyzing all the data from both groups of patients. This analysis describes the pooled PK parameter values.

Statistical Considerations

It is difficult to make rigorous statistical statements (confidence limits, significance, etc.) about population pharmacokinetic parameter estimates. One reason for this is that they are estimates of values rather than of actual observations. Because of this, confidence limits cannot be stated with the same rigor as for actual observations (16). Another reason is that when one uses nonparametric (NP) approaches to population modeling, one can estimate the percentile distances of the estimated distributions, but one cannot make rigorous statements about what the distribution of mean or median parameter values might be with repeated studies, as is the case for the asymptotic confidence limits for parametric approaches to the estimation of assumed Gaussian parameter distributions. Because of this, it is difficult to make much more than suggestive statements about confidence limits or statistical significance using current NP modeling approaches. On the other hand, NP population modeling approaches are proven to be statistically consistent, and are also quite precise (14-15), especially when compared to parametric methods using approximations such as First Order (FO) or First Order, Conditional Estimation (FOCE) methods to compute the likelihoods or conditional probabilities (15). In addition, nonparametric methods can easily discover and quantify unsuspected subpopulations such as fast and slow drug metabolizers.

RESULTS

Twenty patients were studied, 10, randomly selected, in the placebo group, and 10 in the dopamine group. Their mean ages (75 and 74 years) were similar. However, patients in the dopamine group had higher mean weights (75 vs. 65 kg, $P < 0.05$). The mean duration of surgery was not very different between the two groups, (6.2 hours versus 6.7 hours for the placebo and dopamine groups respectively, $P > 0.05$).

The BIGNPAG population parameter estimates are shown in Table 1. Selected marginal densities are shown in Figures 2 - 6. The resulting plots of estimated versus observed serum concentrations are shown in Figure 7.

For the placebo patients, convergence was reached on iteration 2425. The log-likelihood was -101.5087, and gamma was 1.039, suggesting that there was little if any noise in the system other than that of the assay error polynomial. For the dopamine patients, convergence was reached on iteration 1279. The log-likelihood was -64.4838, and gamma was 0.785, again suggesting that there was little noise in the system other than that computed for the assay error polynomial. For the combined patients, convergence was reached on iteration 2680. The log-likelihood was -186.9013, and gamma was 0.925, again suggesting that there was little noise in the system other than that of the assay error polynomial. The low values of gamma strongly suggest that the clinical aspects of the study probably were carried out precisely.

In general, we found a very fast transfer rate constant for lidocaine from the epidural to the serum compartment (K_a part + K_{20}). This mean rate constant was visibly decreased, by over 41%, by dopamine. The mean rate constants for elimination (K_{20}) was 9.7 % higher, and for drug movement from the central to the peripheral compartment (K_{23}) were 47% higher respectively in the dopamine group compared to the placebo group. The rate constant for transfer from the peripheral compartment back to the central compartment (K_{32}) was 46% slower in the dopamine group. The volume of distribution of lidocaine in the central compartment (V_2), was not visibly different between the two groups.

Marginal density plots of the parameter K_a part are shown in Figures 2a and 2b. The dopamine group (Figure 2b) shows a reduction in the ranges and values of K_a part compared to the placebo patients (Figure 2a). Figures 3a and 3b show the distribution of the values of the elimination rate constant K_{20} . This appears to be greater in the dopamine group, as does the rate constant for transfer from the central to the peripheral compartment, K_{23} , as shown in Figures 4a and 4b. While the probability of the various support points in Figures 2-6 all appear to be about 10 %, there are actually small differences in the estimated probabilities of all these points, ranging from 9.73% to 10.26 %. In addition, the distribution is not uniform, as the support points are not equally spaced. What may appear to be outliers in Figures 2-6 are actually the most likely distribution of the support points, since no assumptions of normality or log-normality are made in the NP approach to population modeling. Because of this, any apparent outliers are handled in a straightforward manner, especially in developing the multiple model design of maximally precise dosage regimens.

Figures 5a and 5b show the distributions of the rate constant K_{32} in each group. There is a slight decrease in K_{32} in the Dopamine patients (Figure 5b). Figures 6a and 6b show the distributions of V_2 in the two groups. No visible difference was noted.

The performance of the BIGNPAG population and individualized Bayesian estimation steps are displayed in the plots of the observed versus estimated serum concentrations in Figures 7a and 7b. In the Bayesian step for estimation of individual subject NP parameter values (Figure 7b), the values of the various population support points do not change, but the Bayesian posterior probability of each support point is recomputed using Bayes' theorem, based on the ability of each set of support point parameter values to predict that individual patient's own serum concentrations. Support points that predict that patient's serum concentrations well become much more probable, and those that do not become much less probable. In that way the individualized Bayesian NP posterior joint parameter density is found for each patient. Then the mean values of each patient's Bayesian posterior parameter distribution were used to simulate, estimate, and compare with that patient's own observed serum concentrations (15).

DISCUSSION

To our knowledge, this study represents the first population PK model of epidural lidocaine, using a statistically consistent method and a uniquely identifiable structural model. We used software specifically designed for population pharmacokinetic modeling (13-15). The physiologically necessary (11) peripheral compartment appears not to be associated with any specific effect of lidocaine, but rather to be an overall depot into which the drug equilibrates more slowly.

The most important finding of our analysis is that low-dose dopamine clearly decreases the rate of transfer of lidocaine from the epidural to the serum compartment. Lidocaine apparently moves from the epidural space and the epidural veins to the azygos vein, and then to the superior vena cava (17). It is probable that the low-dose dopamine slows the transfer from the epidural to the serum compartment by causing vasoconstriction of either the epidural veins and/or dural blood flow in general (17). Addition of epinephrine to local anesthetic solutions is also an established tool which anesthesiologists use to slow local anesthetic absorption (10). Dopamine also appears to increase both the rate of elimination of lidocaine and also its rate of transfer from the central (serum) to the peripheral compartment, presumably by increasing tissue perfusion.

Comparing Results of Others

In comparing our results with those of others, we found several significant differences, some of which appear to be due to differences in design and analysis of the various PK studies, the

structural PK models used, the dosing strategies employed, and the interpretation of the results. For example, Downing et al (18) studied epidural lidocaine in women having Caesarian sections. In making their model, they analyzed only the terminal logarithmic phase of serum concentration data points and used the old method of unweighted linear regression on the logarithms of the measured concentrations. They described their results using volume of distribution, clearance, and $T_{1/2}$. They did not use a full structural model. There was no opportunity in their study to perceive the dynamics of the movement of lidocaine through various compartments. They did not use a peripheral compartment, though their data (their figure 1) strongly suggest its presence, with a logarithmic decay having two distinct slopes. Their different structural model, and their very different and less capable analytic method and weighting scheme, gave them quite different, and less definitive, results.

In a previous study of intravenous lidocaine in patients requiring it for arrhythmias (11), usually in a coronary care setting, the pharmacokinetic model had a central (serum) compartment and a tissue (nonserum) compartment. The elimination half time of lidocaine in that study was considerably shorter, ranging from 0.406 hours for a patient with a fairly normal cardiac index of 3.72 L/min/m², to 1.302 hours in a patient with a very low cardiac index of 1.16 L/min/m². In contrast, we found in the present study much slower elimination half-times of 2.24 hours in the placebo patients and 2.04 hours in the dopamine patients. These findings are similar to those of Doherty et al (19) who also found slower disposition and elimination of lidocaine when given by the epidural route.

Lidocaine metabolism is very strongly related to hepatic blood flow (22-24). Any factor associated with slowing of hepatic circulation may affect its pharmacokinetics (4,25). Abernethy and Greenblatt (26) showed that male volunteers over age 65 had a 35 percent reduction in apparent lidocaine clearance. This may be explained by the age-related decrease in cardiac output and associated decrease in hepatic blood flow in elderly patients (27,28). Hepatic blood flow may also be decreased during epidural anesthesia despite maintenance of normotension (8), or by blockade of the splanchnic sympathetic nerves, i.e., epidural blockade that reaches T₅ thoracic dermatome reduces splanchnic perfusion (29). Therefore, infusion of lidocaine during continuous epidural anesthesia may result in high serum lidocaine concentrations, especially in elderly patients. In addition, any other disease associated with a decrease in liver blood flow such as heart failure or β -adrenergic blockers (6,24) may affect elimination of lidocaine from the central compartment. And vice versa, any maneuver that causes an increase in blood flow to the liver may decrease serum lidocaine levels. Since low-dose dopamine selectively increases mesenteric circulation (8,30), it may simultaneously increase blood flow to the liver, and consequently increase lidocaine elimination (9,31), while at the same time slowing transfer of lidocaine from the epidural to the central compartment.

When taken orally, lidocaine has a high hepatic extraction ratio (4) with a fast, liver-dependent first-pass elimination (25). Given intravenously, a bolus lidocaine injection has been described by a two-compartment pharmacokinetic model with a fast distribution phase (half-life 8 min), and slower elimination phase (half-life, 100 min) (31). Several authors have shown that the clearance of lidocaine after a single bolus dose was approximately equal to hepatic blood flow rate (6,22,23). However, during prolonged intravenous infusion in normal volunteers (6,23) the calculated clearance rate was only 25 to 50 percent of hepatic blood flow. This suggests that continuous infusion of lidocaine may somehow slow its kinetics and reduce apparent clearance, or, probably more likely, that lidocaine continues to equilibrate into a slower-exchanging peripheral nonserum compartment (11), and as described by us here. This may explain the higher than expected average serum lidocaine concentrations later on in both our placebo and dopamine groups (5). Accumulation of lidocaine during continuous infusions has been previously reported (11,23,32). LeLorier et al. (32) have shown that apparent lidocaine clearance decreased 52 percent during long-term infusion compared to during short-term

infusion, and lidocaine hepatic extraction decreased 31 percent, which might account for most of the change in clearance. The mechanism responsible for lidocaine accumulation during prolonged continuous infusion might be related either to “alteration” in hepatic cytochrome P₄₅₀ behavior during prolonged administration, saturation of hepatic enzymes responsible for lidocaine metabolism, or, probably most likely, to continued slow equilibration with a deeper peripheral nonserum compartment (11), as also modeled by us in the present analysis. Despite the fact that low-dose dopamine increases both central and tissue blood flows (and therefore liver blood flow) (8,33), we could not firmly demonstrate more than a mild dopamine-associated effect on lidocaine elimination. Therefore, higher than expected lidocaine serum concentrations in both study arms may be explained either by limited elimination due to saturation of hepatic enzymes during prolonged lidocaine administration, or, probably most likely, by continued equilibration into a peripheral compartment (11), as modeled by us here.

The Issue of Biphasic Absorption

Doherty et al (19) studied dogs, and used essentially an epidural bolus given over only 30 seconds, in contrast to the prolonged epidural infusion employed in our study. They described biphasic absorption of epidural lidocaine. They also reported “flip-flop” kinetics in their results. In contrast, our model was specifically set up to avoid the problem of flip-flop behavior. The biexponential model used by them employed biphasic absorption into a single central (serum) compartment, but without any peripheral compartment. It may well be impossible to distinguish between biphasic absorption into a single central compartment with a flip flop, as described by them, or monophasic absorption into a compartment of a model without a flip flop, but having an additional peripheral compartment, as employed by us. One might compare their Figure 2, with its 2 slopes of absorption, with our Figures 8 and 9, which depict a simulated short epidural bolus moving from the epidural compartment 1 into the central (serum) compartment 2, with distribution out to and back from the peripheral compartment 3. Figures 8 and 9 show first a rapid, then a slower, decrease in the amount of drug in the epidural compartment due to the distribution from the epidural to the central compartment.. The three graphs (their Figure 2 and our Figures 8 and 9) appear indistinguishable in form. The elimination curve from the epidural compartment in Figures 8 and 9 is the inverse of the curve of uptake from epidural to serum compartment in their Figure 2. Because of this, biphasic absorption was not needed by us to describe the behavior of epidural lidocaine using the model we employed, as the parameters of exchange to and from the peripheral compartment performed the same function.

Burm et al. (20) also examined epidural lidocaine. They used a biexponential model and also assumed biphasic first order absorption from epidural administration by parallel fast and slow absorption pathways. They used unweighted nonlinear least squares fitting to analyze the data of each patient separately. A short epidural infusion of only 20 seconds was used for unlabeled lidocaine, and a short 10 minute intravenous infusion of deuterium labeled lidocaine was then given. Similar findings were described by Burm in a review article (21). Their extremely short dosage strategy and their data weighting strategy both were very different from the prolonged epidural administration over several hours in the surgical patients described in our present study, along with the more realistic weighting of our data by the assay error polynomial and the estimation of gamma. Again, using our model, it was not necessary to invoke any biphasic absorption to describe the data adequately.

It is highly likely that our study was underpowered (not enough subjects) to detect smaller differences in parameter values between the placebo and dopamine patients. In addition, the average serum lidocaine levels in the two groups were not very different, despite the fact that patients in the dopamine group appeared to require more lidocaine to maintain the same clinical level of analgesia. This issue required further investigation.

In their earlier report (5) the authors observed that through the first hour of anesthesia, the dopamine patients required 13 percent more lidocaine, and over the entire duration of anesthesia, on an hourly basis, the dopamine group required 29 percent more lidocaine to maintain the same clinical analgesic level. At that time (5) they could not offer a plausible explanation of why low-dose dopamine was associated with an apparent increased requirement for epidural lidocaine. Drugs that slow the elimination of lidocaine from the epidural space, in this case, dopamine, should theoretically increase the duration of anesthetic block.

In a further analysis of this problem, all patient data files were reviewed. The placebo patients received an average total lidocaine dose of 1,656 mg given over an average of 6.2 hours, or 267.26 mg/hour. The dopamine patients did receive more lidocaine, 1,947 mg average total, 17% more, but over a longer average period of time, 6.7 hours, for a slightly higher average rate of 290.297 mg/hour. However, after correcting for body weight, the placebo patients received $267.226 / 65 = 4.111$ mg/kg/hour, while the dopamine patients received $290.297 / 75 = 3.871$ mg/kg/hour, somewhat less.

A Simulation Study

Because of the complexity of the model with its many combinations of parameter values, it was not clear just how lidocaine would move through the model. For example, would the decreased K_a or the increased K_{20} with dopamine have the greater influence on the serum lidocaine amounts in compartment 2? What would happen with equilibration into peripheral compartment 3?

To answer such structural questions, simulation analyses were conducted to compare the relative behavior in the dopamine vs. placebo patients. In one simulation, the mean parameter values were used. In another, the median values were used. The results were not visibly different, so only results using the mean values are shown here. In one simulation, a bolus of 400 mg of lidocaine was given into the epidural compartment. In another, the bolus was followed by an epidural infusion of 200 mg/hour for 6 hours. This is similar to the regimen many patients received, although with many variations. The results based on mean parameter values are shown in Figures 8-10. True Monte Carlo simulation based on the overall parameter distributions, to examine variability in response, was not done.

Figure 8a plots the total amount of lidocaine moving through compartments 1, 2, and 3 of the model shown in Figure 1, for 24 hours. In the placebo group, lidocaine rapidly leaves the epidural compartment 1, moving into the serum compartment 2, reaching a peak slightly over 350 mg (5.3 mg/kg or 3.30 mg/L at about 0.08 hours (7.5 min). It then decreases due to both elimination and distribution into the peripheral compartment 3, which reaches a peak of about 80 mg (1.23 mg/kg) at about 1.6 hours. Compartment 1 has almost no drug remaining by 0.25 hrs (15 min). Almost all drug is eliminated from the body by about 20 hours.

Figure 8b, in contrast, shows some major differences with dopamine. Here the disappearance of drug from the epidural compartment is still rapid, but visibly much less so. The amount of lidocaine in serum compartment 2 reaches a lower peak of about 300 mg (4.0 mg/kg or 3.2 mg/L at about 5 minutes), and the amount in the peripheral compartment 3 fills much faster and reaches a peak of about 150 mg (2.0 mg/kg, much more than 1.23 mg/kg in the placebo group) at about 1.3 hours. These relationships are seen more clearly in Figures 9a and 9b, which show only the first two hours of the events shown in Figures 8a and 8b respectively.

Figures 10a and 10b show the results of following the simulated 400 mg bolus followed by an epidural infusion of 200 mg/hour for 6 hours. This regimen approximates what was typically given to many patients. Amounts of epidural lidocaine are low in both cases, but are visibly higher in the dopamine patients throughout the 6 hour infusion. The amount of lidocaine in

serum compartment 2 falls slightly in the placebo patients after its initial peak of about 380 mg, then rises to a final peak of about 560 mg at the end of the 6 hour epidural infusion. The amount in peripheral compartment 3 gradually rises to a peak of about 180 mg at 6 hours.

In contrast, the lidocaine in the dopamine patients reached a lower and later initial peak in serum compartment 2 of about 335 mg at about 15 minutes. The profile of these serum amounts are fairly representative of those concentrations in individual patients, but they varied of course, as each patient actually received a different regimen clinically adjusted to his/her needs. The amount the serum compartment then fell visibly more rapidly than in the placebo group, and finally rose only to about 450 mg at 6 hours. Amounts in peripheral compartment 3 were much greater than in the placebo group, and reached a peak of about 400 mg, slightly more than twice that in the placebo patients.

This simulation study confirms the slower release of lidocaine from epidural compartment 1 in the dopamine patients, the somewhat reduced amount in serum compartment 2, and the much greater amounts in peripheral compartment 3 in the dopamine patients. In addition, the dopamine patients had visibly more lidocaine in the epidural compartment throughout the simulated infusion.

An Unmodeled Compartment - the Cerebrospinal Fluid

A specific compartment to represent the cerebrospinal fluid (CSF) was not included in the model for this study, as there were no direct observations of drug concentrations in the CSF, and there are already two unobserved nonserum compartments in the model - the epidural compartment and the peripheral compartment - whose behavior must be inferred from fitting the data of the measured serum concentrations. A peripheral compartment is physiologically relevant because it is required to describe properly the pharmacokinetic behavior of intravenous lidocaine (11)

Concentrations of lidocaine in the CSF are known to be quite significant after epidural administration. For example, Lund and Cwik (34) found quite high concentrations in the CSF which peaked at or before the first observation at 15 minutes after an epidural bolus of 600 mg of lidocaine. These concentrations were decreased and the CSF peak was delayed by epinephrine. The authors suggested that because of this delayed uptake, more drug should be available for dural penetration or diffusion. This type of behavior can be seen in our study by comparing the simulated amounts of lidocaine in the epidural, serum, and peripheral compartments in Figures 8 a and b and 9 a and b.

Similar delayed and decreased uptake of epidural lidocaine into CSF by epinephrine was described by Lund and Covino (35). They suggested that CSF lidocaine may not simply be the result of diffusion across the dura, but may also be dependent on the amount of drug entering the vascular compartment and then passing by way of the minute dural vessels into the CSF. They concluded that epidural lidocaine is "taken up very rapidly by the blood and also appears soon thereafter in the spinal fluid" (35a, p328).

Our study cannot add to this information about CSF lidocaine. However, concentrations of lidocaine in the peripheral compartment of our model do rise soon after the rapid uptake into the serum compartment, and CSF lidocaine may well be at least one component of this overall peripheral compartment. In addition, dopamine increased the exchange from central to peripheral compartment in our study (K23), and peripheral compartment amounts of lidocaine were significantly increased, rather than decreased, by dopamine. It is therefore likely that the significant amounts of CSF lidocaine found by the above authors (34,35) may be one component of, but clearly not the major component of, the amounts of drug in our peripheral compartment model.

CONCLUSION

In conclusion, the placebo patients received an overall greater weight-adjusted lidocaine infusion rate than did the dopamine patients. This finding is different from that described in the previous study (5), and is consistent with the slowing by dopamine of the overall rapid rate constant from the epidural to the serum compartment, though it was still quite fast. Dopamine increased the rate constant for elimination, and also the transfer from the central to the peripheral compartment, presumably by increasing tissue perfusion. This suggests that low-dose dopamine may increase both systemic and tissue perfusion, and hence may increase lidocaine elimination and exchange from the central to the peripheral (tissue) compartment, while at the same time slowing the movement of lidocaine from the epidural space to the general venous circulation, and keeping more lidocaine in the epidural space during continuous epidural infusion.

Nonparametric population models are extremely well suited for the new method of “multiple model” (MM) dosage design (36-38). The population model described here should be useful in developing maximally precise MM infusion regimens to define and then to achieve desired target goals in the epidural or the serum concentration compartments. Monitoring and adjustment of therapy can be done by checking both pinprick response and serum concentrations using clinical software based on the model described here.

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Figure 1.

Structural model of lidocaine kinetics. Compartment 1 represents the epidural compartment into which lidocaine was injected and infused. Compartment 2 represents the serum concentration compartment. Compartment 3 represents the peripheral (nonserum) compartment. Model parameters are ($K_a \text{ part} + K_{20}$) for absorption from the epidural into the serum concentration compartment (always greater than K_{20} , the elimination rate constant from the central compartment). K_{23} represents the rate constant from the central to the peripheral compartment, K_{32} , the rate constant back from the peripheral compartment, and V_2 , the apparent volume of distribution of the central compartment.

Figure 2a.
Marginal density plot of the parameter K_a part (hr⁻¹). Placebo patients.

Figure 2b. Marginal density plot of the parameter K_a part (hr^{-1}). Dopamine patients. Note the lower parameter values here than in Figure 2a.

Figure 3a.
Marginal density plot of the parameter K20 (hr⁻¹). Placebo patients.

Figure 3b.
Marginal density plot of the parameter K20 (hr⁻¹). Dopamine patients.

Figure 4a.
Marginal density plot of the parameter K23 (hr⁻¹). Placebo patients.

Figure 4b.
Marginal density plot of the parameter K23 (hr⁻¹). Dopamine patients.

Figure 5a.
Marginal density plot of the parameter K32 (hr⁻¹). Placebo patients.

Figure 5b.
Marginal density plot of the parameter K32 (hr⁻¹). Dopamine patients.

Figure 6a.
Marginal density plot of the parameter V2 (L). Placebo patients.

Figure 6b.
Marginal density plot of the parameter V2 (L). Dopamine patients.

Figure 7a.

Scatterplot of estimated versus measured serum concentrations, in ug/ml, based on medians of population parameter distributions. Pooled data of all patients.

Figure 7b.

Scatterplot of estimated versus measured serum concentrations, in ug/ml, based on medians of individual subject Bayesian posterior parameter distributions. Pooled data of all patients.

Figure 8a, left.

Placebo patients. Mean parameter values. Amounts (mg) of drug in epidural compartment 1 (bottom), serum compartment 2 (top), and peripheral compartment 3 (middle) simulated from a 400 mg epidural bolus into epidural compartment 1 at time 0. Time from 0 to 24 hours.

Figure 8b, right.

Dopamine patients. Same simulation. See text for discussion.

Figure 9a, left.

Same data as in Figure 8a, showing apparent biphasic, but here monophasic, epidural disappearance during the first 2 hours.

Figure 9b, right.

Same data as in 8b, showing apparent biphasic, but here monophasic, epidural disappearance during the first 2 hours.

Figure 10a, left.

Placebo patients, mean parameter values. Simulation of results from a representative regimen received by the patients, consisting of an epidural bolus of 400 at time 0.0, followed by of an epidural infusion of 200 mg/hour for 6 hours. Again, amounts (mg) in epidural compartment 1 (bottom), in serum compartment 2 (top), and in peripheral compartment 3 (middle). Time 0 to 24 hrs.

Figure 10b, right.

Dopamine patients, mean parameter values. Simulated results of the same bolus followed by the same infusion for 6 hours. Amounts (mg) in epidural compartment 1 (bottom), serum compartment 2 (top), and in the peripheral compartment 3 (middle). See text for discussion.

Table 1

Mean, median, standard deviation, and % coefficient of variation (CV) of pharmacokinetic parameters for the placebo, dopamine, and combined placebo and dopamine groups

Parameter	Mean	Median	SD	% CV
Ka part (hr⁻¹)				
Placebo	37.791	22.723	42.232	111.751
Dopamine	16.604	13.394	11.078	66.719
All patients	33.569	18.840	42.250	125.860
K20 (hr⁻¹)				
Placebo	0.3098	0.3379	0.0644	20.788
Dopamine	0.3399	0.3041	0.0985	28.979
All patients	0.3189	0.2995	0.0703	22.044
K23 (hr⁻¹)				
Placebo	0.9377	0.2024	1.6024	170.886
Dopamine	1.3784	0.6295	2.4894	180.600
All patients	1.2736	0.5847	2.0960	164.572
K32 (hr⁻¹)				
Placebo	2.8161	0.5581	4.3401	154.117
Dopamine	1.5237	0.4125	3.2954	216.276
All patients	2.1861	0.4389	3.9000	178.400
Volume of Distribution of Compartment 2 (L)				
Placebo	106.2905	88.7317	40.6795	38.2720
Dopamine	94.6621	91.0094	32.7763	34.6245
All patients	98.8996	90.7130	34.4857	34.8694