Anesthesiology 2001; 94:566–73

Modeling Population Pharmacokinetics of Lidocaine

Should Cardiac Output Be Included as a Patient Factor?

Jette A. Kuipers, M.Sc.,* Fred Boer, M.D., Ph.D.,† Annemiek de Roode, M.D., Ph.D.,† Erik Olofsen, M.Sc.,‡ James G. Bovill, M.D., Ph.D., F.F.A.R.C.S.I.,§ Anton G. L. Burm, Ph.D.§

Background: **Inclusion of cardiac output and other physiologic parameters, in addition to or instead of, demographic variables might improve the population pharmacokinetic modeling of lidocaine.**

Methods: **Thirty-one patients were included in a population pharmacokinetic study of lidocaine. After bolus injection of lidocaine (1 mg/kg), 22 or 10 blood samples per patient were taken from a radial artery. During the experiment, cardiac output was measured using a thoracic electrical bioimpedance method. The following four population pharmacokinetic models were constructed and their performances investigated: a model with no covariates, a model with cardiac output as covariate, a model with demographic covariates, and a model with both cardiac output and demographic characteristics as covariates. Model discrimination was performed with the likelihood ratio test.**

Results: **Inclusion of cardiac output resulted in a significant improvement of the pharmacokinetic model, but inclusion of demographic covariates was even better. However, the best model was obtained by inclusion of both demographic covariates and cardiac output in the pharmacokinetic model.**

Conclusions: **When population pharmacokinetic models are used for individualization of dosing schedules, physiologic covariates, *e.g.*, cardiac output, can improve their ability to predict the individual kinetics.**

IN recent years, population pharmacokinetic models have become popular. With this approach, patient factors such as age, gender, and body weight can be incorporated with the aim of enhancing the predictive value of the model, making it useful in a wide population of patients. Population pharmacokinetic data with inclusion of demographic data have been reported for a wide variety of anesthetics.[1]

Few studies have included physiologic parameters, although these could be more useful for individualization compared with demographic data alone. It has been suggested that in addition to age, gender, and weight, blood flow should be included as a population parameter if possible.[2] Cardiac output has been found to largely determine the intercompartmental clearance (*i.e.*, tissue distribution) of alfentanil in humans.[3] Cardiac output is a potentially valuable parameter for describing the relation between physiology and pharmacokinetics. This is especially true for drugs with a high extraction ratio.[4] Knowledge of the influence of physiology on the pharmacokinetics in the individual patient could contribute to the prediction of the pharmacokinetic parameters of a drug in that patient and therefore to the individualization of dosing schemes.

A drawback that limits the inclusion of cardiac output in population pharmacokinetic studies is that most reliable techniques for measuring cardiac output are invasive. New developments, such as pulse dye densitometry,[5,6] an improved version of the noninvasive bioimpedance cardiac output monitor,[7] and cardiac output measurement based on a partial carbon dioxide rebreathing technique,[8] may offer new possibilities.

In the current study we investigated the pharmacokinetics of lidocaine using a population pharmacokinetic model with and without the inclusion of cardiac output, measured with a bioimpedance method, and demographic variables. Lidocaine was chosen as a model drug because its tissue distribution is perfusion-limited and it has a high hepatic extraction ratio, so that both its distribution and elimination are likely to depend on cardiac output.[4]

Materials and Methods

Experimental Protocol

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center. The study included 31 patients, American Society of Anesthesiology physical status I and II, undergoing ophthalmic surgery with general anesthesia. Informed consent was obtained from each patient. Exclusion criteria were a history of cardiovascular disease, *i.e.*, hypertension, cardiac failure, recent myocardial infarction (< 6 months), or the use of cardiovascular medication; diabetes mellitus; allergy for local anesthetics of the amide type; cardiac conduction disorders; and participation in other studies.

Patients were premedicated with 7.5 mg midazolam orally 60 min before anesthesia. Before anesthesia, electrocardiogram electrodes were placed, and a peripheral intravenous infusion was established. A pulse oximeter was connected for the measurement of arterial oxygen saturation. During local anesthesia with 1% mepivacaine, a 22-gauge catheter was placed in a radial artery. Cardiac

* Research Fellow, † Staff Anesthesiologist, ‡ Research Associate, § Professor of Anesthesiology.

Received from the Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands. Submitted for publication March 6, 2000. Accepted for publication November 14, 2000. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Burm: Department of Anesthesiology (P-5), Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. Address electronic mail to: A.G.L.Burm@ LUMC.nl. Reprints will not be available from the authors. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

output was measured continuously using a thoracic electrical bioimpedance device (IQ Renaissance Technologies Inc., Newtown, PA). The cardiac output data were stored on the hard disk of the cardiac output computer for off-line analysis.

Patients received propofol with a target-controlled infusion and remifentanil with a manually controlled syringe pump for both induction and maintenance of anesthesia. Target concentrations of propofol were 3–5 μg/ml, and the infusion rates of remifentanil were 6–20 $\mu g \cdot kg^{-1} \cdot h^{-1}$. When the patient had lost consciousness, a bolus dose of 1 mg/kg lidocaine was given. For muscle relaxation, 0.1 mg/kg cisatracurium was given, and repeat doses were given as necessary.

Blood sampling was from the radial artery catheter. Before the experiments, a blood sample of 20 ml was drawn for construction of the calibration curve of lidocaine. In 11 patients, 22 blood samples (5 ml) were drawn at 0.5, 1, 2, 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 270, 300, and 360 min. In 20 patients, 10 blood samples (5 ml) were taken, to meet the requirement of at least one sample per estimated parameter[9] in the pharmacokinetic analysis, which was performed with a two- or three-compartment model (four or six parameters). The sampling schedule of these blood samples was randomized such that in each patient, at least three samples were collected in each of the following three time intervals: 1–10 min, 11–60 min, and 61–360 min after the bolus injection. The total blood sampling period represents three to four times the elimination half-life of lidocaine.[10] All 31 patients were included in the population pharmacokinetic analysis.

Analytical Methods

Lidocaine concentrations in whole blood were measured by a modified gas liquid chromatography method (see Appendix).[10] Concentrations were measured at the Anesthesia Research Laboratory, Leiden University Medical Center, Leiden, The Netherlands.

Data Analysis

Population pharmacokinetic data of all 31 patients were determined using NONMEM (Version V, level 1.1).[11] NONMEM analysis was performed using a prediction subroutine configured with a log-normal variance model for the interindividual error term of the kinetic parameters [V_1, V_2, V_3, CL, CL(rapid distribution) and CL(slow distribution)]) and, when included, covariates that were normalized and centered around the median:

$$\theta_i = \theta_{TV} \cdot e^{\eta_i} \cdot \left(1 + \sum_{j=1}^{m} \theta_{cov_j}\left(\frac{cov_{ji}}{MD\ cov_j} - 1\right)\right)$$

where θ_i is the value of the pharmacokinetic parameter in individual i, θ_{TV} is the typical value of the pharmacokinetic parameter in the population, η_i is the Bayesian estimate for the random variable η in individual i with mean zero and variance ω^2, θ_{covj} is the value of the parameter (coefficient) describing the dependence of the pharmacokinetic parameter on covariate j, cov_{ji} is the value of the covariate j in individual i, $MDcov_j$ is the median value of the covariate j in the population, and m is the number of covariates included. A constant coefficient of variation model was used for the residual intraindividual error. The pharmacokinetic analysis without inclusion of covariates was performed with a three- or two-compartment model. The choice between the two- and three-compartment models was made using the likelihood ratio test, which favored the three-compartment model (model A). Therefore, a three-compartment model was used for further data analysis with inclusion of covariates. The inclusion procedure of the covariates age, gender, weight, Quetelet index (weight/length^2), and cardiac output in the population models is described below. The following models were examined: models that included the cardiac output (model B), models that included demographic variables (model C), and models that included both cardiac output and demographic variables (model D). The value of the cardiac output was the mean cardiac output measured between the time of the bolus injection and the collection of the last blood sample in that patient.

Bias and inaccuracy were examined to assess the performances of the models with and without inclusion of the different covariates. The performance error was calculated for each blood sample as:

$$PE = (C_p - C_{pred})/C_{pred} \cdot 100$$

where C_p is the measured concentration of lidocaine, and C_{pred} is the corresponding predicted concentration. For each patient, the bias of the model was expressed as the median PE (MDPE) and the inaccuracy as the median of the absolute values of the PE (MDAPE) over all blood samples collected from that patient. The MDPE and MDAPE for the entire population were calculated as the weighted (by the number of samples) mean of the individual MDPE and MDAPE from all blood samples.[12]

Inclusion Procedure for Covariates

Covariates were sequentially added to the model, *i.e.*, one covariate was added to one pharmacokinetic parameter in each subsequent step. First, the model parameters of the population pharmacokinetic model were estimated without inclusion of covariates, as described above. Using the equation for θ_i and the log-normal variance model, the individual Bayesian estimates of the pharmacokinetic parameters were determined for the 31 patients. Subsequently, the linear correlations between the individual Bayesian estimates of the pharmacokinetic parameters and the demographic variables, *i.e.*, weight,

Table 1. Patient Characteristics

Variable	All Patients	Patients Stratified by Gender	
		Men	Women
Number of patients	31	17	14
Age (yr)	45 (19–76)	33 (19–76)	46 (19–68)
Weight (kg)	75 (51–102)	80 (70–102)	74 (51–90)*
Quetelet index (kg/m^2)	24.8 (20.4–33.3)	24.8 (21.6–33.3)	24.8 (20.4–30.5)
BSA (m^2)	1.9 (1.5–2.2)	2.0 (1.8–2.2)	1.8 (1.5–2.0)*
CO (l/min)†	5.8 (3.6–10.0)	6.6 (4.6–10.0)	4.8 (3.6–6.6)*

* $P < 0.05$ *versus* males. Data are median (range). † Cardiac output values are mean values measured between the time of the bolus injection and the collection of the last blood sample.

BSA = body surface area; CO = cardiac output.

age, gender, Quetelet index, and/or cardiac output, were tested using the statistical software package SPSS (release 9.0.0, SPSS Inc., Chicago, IL). The variable that showed the most significant correlation with any pharmacokinetic parameter was then included in the model as a covariate of that parameter, and the model parameters were again estimated. The significance of the inclusion of the covariate was assessed with the likelihood ratio test. This procedure was repeated until inclusion of an additional covariate no longer produced significant improvement of the model.

Computer Simulations

To further explore the possible implications of the findings of this study, various computer simulations were performed using a spreadsheet program (Microsoft Excel 97; Microsoft Corporation, Redmond, WA). These were focused on the role of cardiac output and body weight during a clinically used dosing regimen, *i.e.*, a rapid (50 mg/min for 2 min) followed by a slower (2.5 mg/min for 12 h) intravenous infusion of lidocaine.

Statistics

Patients' characteristics are summarized as mean ± SD. Differences between males and females were examined using the two-sample Student *t* test. Pharmacokinetic parameters are summarized as typical values and SEs, and interindividual variability as coefficient of variation, calculated as the square root of the variance ω^2 of η (see data analysis). Model discrimination was performed using the likelihood ratio test. $P < 0.05$ was considered significant, except where stated otherwise.

Results

The characteristics of the 31 patients are presented in table 1. Mean cardiac output and weight were higher in male than in female patients. There were no correlations ($R^2 < 0.1$; $P > 0.1$) between cardiac output and age, weight, or Quetelet index. Quetelet index correlated with weight ($R^2 = 0.72$; $P < 0.0001$) but not with age or gender. The mean cardiac output, measured between the time of the bolus injection and the collection of the last blood sample, varied from 3.6 to 10.0 l/min. Cardiac output also was reasonably stable over time: coefficients of variation reflecting the intraindividual variation in mean cardiac output over consecutive 1-h periods ranged from 2 to 24% (mean, 9%).

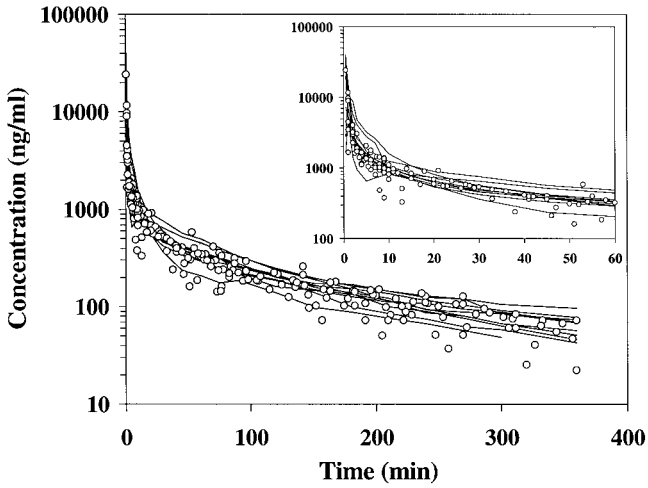

Fig. 1. The whole-blood lidocaine concentration–time profiles. Concentrations in the 10 patients in whom 22 blood samples were taken are presented as thin lines connecting individual data points. Concentrations in the patients in whom only 10 blood samples were collected are shown as open circles. The inset shows the concentrations during the first hour after the administration.

Measured lidocaine concentrations *versus* time are shown in figure 1. The three-compartment population pharmacokinetic model described the concentration–time profiles significantly better than a two-compartment model according to the likelihood ratio test. The values of the parameters of the three-compartment models with and without identified significantly contributing covariates are presented in table 2, together with the SEs and the interindividual coefficients of variation. Intraindividual coefficients of variation were similar (13%) with all four models. The $-2 \cdot \log$ likelihood values for the different models are also shown in table 2. Inclusion of cardiac output (model B) resulted in a significant improvement of the model compared with model A. Inclusion of demographic covariates (model C) not only resulted in a significant improvement over model A, but also over model B. However, inclusion of cardiac output in addition to demographic covariates (model D) resulted in a significant improvement over models A, B, and C, illustrating the additional information of cardiac output, *i.e.*, demographic data do not completely account for the influence of cardiac output. The effects of the covariates on the pharmacokinetic parameters of the different models are presented in table 3.

The bias and the inaccuracy of the four models were determined for all patients. The individual biases and

Table 2. Pharmacokinetic Parameters of the Four Models and Parameters (Coefficients) Describing the Dependence of the Pharmacokinetic Parameters on Covariates

	Model A	Model B	Model C	Model D
Number of parameters (θ)	6	8	11	13
$-2 \cdot$ log likelihood	4,274	4,261*	4,232*†	4,219*‡
Pharmacokinetic parameters (θ_{TV})				
V_1 (l)	1.29 ± 0.21 (44)	1.30 ± 0.27 (44)	1.31 ± 0.15 (42)	1.29 ± 0.14 (42)
V_2 (l)	7.39 ± 1.40 (32)	7.70 ± 1.81 (31)	8.05 ± 0.94 (38)	8.04 ± 0.90 (34)
V_3 (l)	57.3 ± 4.0 (24)	57.4 ± 4.2 (24)	56.8 ± 3.0 (20)	56.7 ± 2.9 (20)
CL (l/min)	0.646 ± 0.027 (18)	0.647 ± 0.028 (16)	0.646 ± 0.021 (16)	0.647 ± 0.019 (14)
CL (rapid distribution; l/min)	0.898 ± 0.138 (19)	0.918 ± 0.195 (19)	1.010 ± 0.082§	0.997 ± 0.081§
CL (slow distribution; l/min)	0.750 ± 0.074 (25)	0.745 ± 0.079 (25)	0.752 ± 0.052 (12)	0.751 ± 0.053 (12)
Coefficients (θ_{covi})				
CO (*vs.* V_2)	—	0.698 ± 0.259	—	0.725 ± 0.255
CO (*vs.* CL)	—	0.378 ± 0.149	—	0.312 ± 0.108
QI (*vs.* V_3)	—	—	0.835 ± 0.296	0.841 ± 0.289
QI (*vs.* CL [slow distribution])	—	—	0.726 ± 0.358	0.720 ± 0.349
Weight (*vs.* CL)	—	—	0.600 ± 0.120	0.475 ± 0.164
Age (*vs.* CL [rapid distribution])	—	—	−0.704 ± 0.109	−0.702 ± 0.103
Age (*vs.* CL [slow distribution])	—	—	−0.639 ± 0.132	−0.640 ± 0.124

Data are (typical) values ± SE. Data in brackets are interindividual coefficients of variation (%).

* $P < 0.01$ *versus* model A. † $P < 0.01$ *versus* model B. ‡ $P < 0.01$ *versus* models B and C. § Interindividual coefficient of variation could not be estimated, *i.e.*, it does not contribute significantly to the statistical model.

V_1 = volume of the central compartment; V_2 = volume of the shallow peripheral compartment; V_3 = volume of the deep peripheral compartment; CL = elimination clearance; CO = cardiac output; QI = Quetelet index.

Table 3. The Influence of Covariates on the Pharmacokinetic Parameters for Models B, C, and D

Parameters	Equation
Model B	
V_2	$2.33 + 0.928 \times CO$
CL	$0.402 + 0.0422 \times CO$
Model C	
V_3	$9.37 + 1.91 \times QI$
CL	$0.258 + 0.00517 \times$ weight
CL (rapid distribution)	$1.721 - 0.0158 \times$ age
CL (slow distribution)	$0.687 - 0.0107 \times$ age $+ 0.0220 \times QI$
Model D	
V_2	$2.21 + 1.01 \times CO$
V_3	$9.02 + 1.92 \times QI$
CL	$0.138 + 0.00410 \times$ weight $+ 0.0349 \times CO$
CL (rapid distribution)	$1.697 - 0.0156 \times$ age
CL (slow distribution)	$0.691 - 0.0107 \times$ age $+ 0.0218 \times QI$

Pharmacokinetic parameters that are not shown were not influenced by covariates and were equal to the typical value shown in table 2.

V_2 = volume of the shallow peripheral compartment; V_3 = volume of the deep peripheral compartment; CO = cardiac output; CL = elimination clearance; QI = Quetelet index.

inaccuracies are shown in figure 2. Weighted mean biases and inaccuracies over all patients were similar with the four models. Although the weighted mean MDPE and MDAPE were overall similar with models A and D, in 21 of 31 patients the bias and inaccuracy were less when using model D. Model D resulted in a better prediction in 9 of the 10 patients, which showed the largest bias and inaccuracy with model A.

The computer simulations showed that in the average patient with a normal (6 l/min) cardiac output, the predicted blood concentration–time profiles during prolonged infusion of lidocaine were very similar with all four models (fig. 3). However, when cardiac output is lower than normal, concentrations predicted by models B and D, which include cardiac output as a covariate, are considerably higher than those predicted by models A and C. Conversely, when cardiac output is higher than normal, the concentrations predicted by models B and D are considerably lower than those predicted by models A and C. In patients with average body weight, concentrations predicted by models B and D are very close, irrespective of the cardiac output. On the other hand, if the patient's body weight deviates considerably from the average but its cardiac output is close to normal, concentrations predicted by model C are closer to those predicted by model D than those predicted by model B. However, if cardiac output is also altered, the picture becomes more complex and interesting, as covariates may enhance or antagonize each other's influences. In general, concentrations predicted by the four models diverge more as body weight and cardiac output deviate more from the average values. In addition, variations in age and Quetelet index also affect the predicted plasma concentration–time profiles. However, these variables do not affect the elimination clearance and, therefore, the steady state concentrations achieved.

Discussion

Cardiac output is a significant determinant of the pharmacokinetics of many drugs, in particular if the distribution and elimination are perfusion-limited.[4,13–15] The primary objective of the current study was to investigate

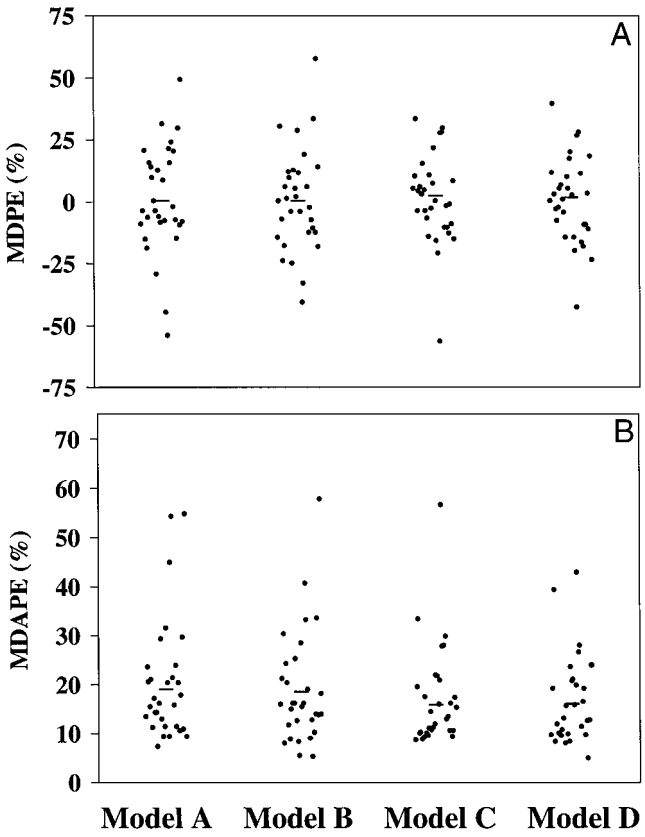

Fig. 2. (*A*) Median performance error (MDPE, bias) for individual patients (●) for the four models and the weighted mean of the 31 patients (—). (*B*) Median absolute performance error (MDAPE, inaccuracy) for individual patients (●) for the four models and the weighted mean of the 31 patients (—).

whether the inclusion of cardiac output as a covariate instead of or in addition to demographic variables in the population pharmacokinetic modeling of lidocaine might improve the predictive value of the model. To this end, we constructed and evaluated four different mixed-effects models with and without different covariates. The study showed that the pharmacokinetics of lidocaine are best described when both demographic parameters and cardiac output are included in the model. We also found that demographic parameters cannot substitute for cardiac output. Thus, cardiac output provides additional information over and above the usual demographic parameters.

The population models that included cardiac output showed a distinct dependence of the elimination clearance on cardiac output. This is not surprising, because lidocaine has a high hepatic extraction ratio and, therefore, its clearance will be highly dependent on liver perfusion and thus cardiac output. Perhaps more surprising is the observation that cardiac output markedly affects the volume V_2, with no significant effects on the intercompartmental clearances. This may be related to the inherent limitations of compartmental models. In the body, an increase in blood flow to any tissue will increase the rate of delivery of drug to that tissue. If there are no diffusion limitations, such as is the case with lidocaine, the concentration in that tissue will increase and decrease more rapidly if the blood flow to that organ is increased, *i.e.*, the distribution clearance to and from that tissue will increase with blood flow. However, the compartments of conventional compartmental models are not synonymous to specific tissues or tissue groups. Keeping this in mind, it is conceivable that an increase in blood flow to a specific tissue, *e.g.*, muscle, will cause a shift in the volumes of the compartments, *e.g.*, from compartment 3 to compartment 2, as observed in the current study (note that a small shift of, *e.g.*, 4 l, causes a profound increase in V_2, which is readily detected, but only a small decrease in V_3, which may remain undetected). Even with the increased cardiac output, the distribution clearance to the specific tissue may be small compared with the clearances to other tissues in compartment 2, such that the average rapid intercompartmental distribution clearance remains virtually unchanged. In addition, a higher cardiac output does not mean that blood flows to all tissues are increased proportionally. This further complicates the prediction and interpretation of the (lack of) influence of cardiac output on the distribution clearances in conventional compartmental models.

The population parameters for model A can be compared with the parameters reported by Dyck *et al.*,[16] who performed a similar data analysis on arterial blood concentrations obtained from 12 healthy subjects. These subjects were given lidocaine by target-controlled infusion for 75 min, whereby the target concentration was increased from 1 to 5 ng/ml in steps of 1 ng/ml, and each target was maintained for 15 min; blood samples were obtained frequently, both during and after the infusion. The elimination clearance (CL = 0.703 l/min) reported by Dyck *et al.*[16] is comparable to the value found in the current study. However, the other parameters [V_1 = 6.99 l; V_2 = 12.2 l; V_3 = 134 l; CL(rapid distribution) = 1.24 l/min, CL(slow distribution) = 1.49 l/min] differed considerably from those found by us (table 2). To further compare the parameters found by Dyck *et al.*[16] with the parameters we found, both data sets were used to simulate a concentration–time profile after a bolus injection of 75 mg, which equals the median dose in the current study. The results of these simulations are shown in figure 4, and they predict concentration–time profiles that, based on the data of Dyck *et al.*, are overall somewhat lower during most of the distribution phase and higher during the terminal elimination phase.

The differences in the typical values of the parameters reported by Dyck *et al.*[16] and in the current study may be related to differences in patient characteristics, in particular body weight, which was considerably greater and more variable in the study by Dyck *et al.* (mean ± SD, 92 ± 34 kg; range, 57–187 kg) than in the current study (mean ± SD, 77 ± 12 kg; range, 51–102 kg) and pre-

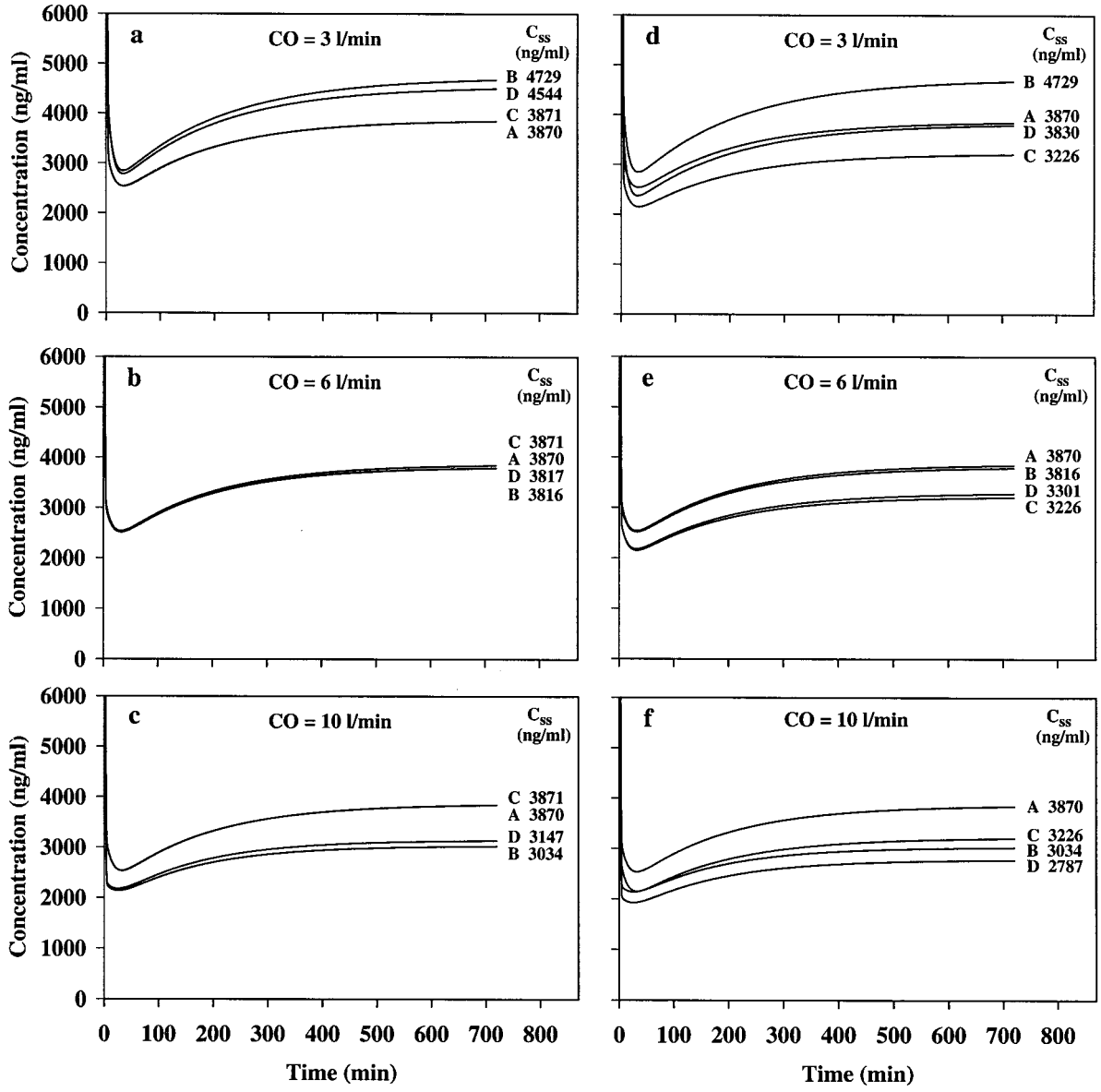

Fig. 3. Simulations of blood concentration–time profiles of lidocaine during continuous intravenous infusion (infusion rates: 50 mg/min during the first 2 min, then 2.5 mg/min). (*Left*) Concentrations in the "average" patient (age, 45 yr; weight, 75 kg; Quetelet index; 25 kg/m^2). (*Right*) Concentrations in a relatively heavy patient (age, 45 yr; weight, 100 kg; Quetelet index, 30 kg/m^2). Cardiac output (CO) values are shown in each panel. Ultimately achieved steady state concentrations (C_{ss}) are also shown in each panel.

sumably also to differences in Quetelet index (not reported by Dyck *et al.*). Differences in parameters characterizing the early distribution may, in part, also be related to differences in the mode of administration (target-controlled infusion *vs.* bolus injection). However, other studies with lidocaine have shown that its pharmacokinetics after bolus injection is comparable with the pharmacokinetics of a bolus injection, followed by an infusion in humans[17] and monkeys.[18]

The results of the current study are in good agreement with population pharmacokinetic study by Vozeh *et al.*,[19] which showed a 46% reduction in elimination clearance of lidocaine in patients with congestive heart failure. The same study also showed a 24% reduction in V_1 in patients with congestive heart failure, whereas based on the current study, a reduction in the volume of V_2 is predicted in patients with a reduced cardiac output. Considering that the study by Vozeh *et al.*[19] was based on a two-compartment model, these observations also appear to be in good agreement.

The rationale behind population pharmacokinetics is that the inclusion of demographic variables, *e.g.*, age, weight, and gender, allows individualization of a pharmacokinetic model. However, gender- and age-related differences in dose requirements may not be related to age and gender *per se* but to other patient characteristics that depend on age or gender,[20] *e.g.*, cardiac output. Changes in cardiac output, and hence hepatic and renal

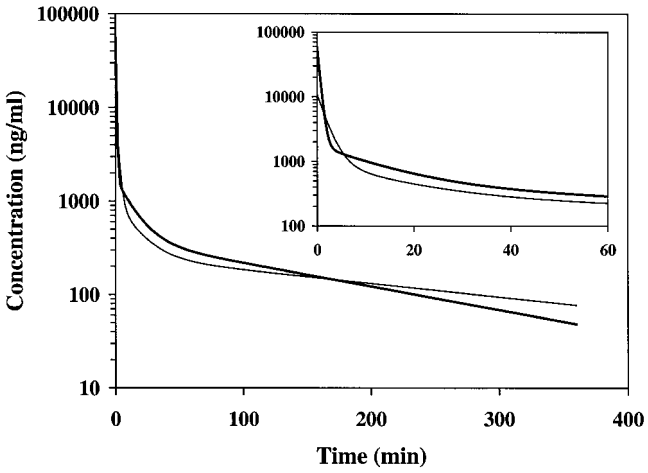

Fig. 4. Simulation of the lidocaine concentration–time profile after a bolus dose of 75 mg with the parameters found in this study for model A (thick line) and those reported by Dyck *et al.*[16] (thin line). The inset shows the concentrations during the first hour after the administration.

blood flows, have important implications for anesthesia. Gender-related differences in the pharmacokinetics of thiopental were identified as being related to differences in blood flow and body mass.[21] Some of the other gender-related differences are possibly also a result of differences in cardiac output.[22,23] In addition, cardiac output is often thought to decrease with increasing age, although different studies showed opposing results. Brandfonbrener *et al.*[24] reported a very strong negative correlation between cardiac output and age in men. These observations were supported by a subsequent study in both men and women.[25] However, another study that included only healthy older people found no relation between cardiac output and age.[26] Therefore, aging itself cannot generally be isolated as the sole biologic factor explaining the association of altered pharmacokinetics with age. Changes with age may be statistically significant but may not be of clinical importance because they may be small compared with the interindividual variability independent of age.[27]

Model C, which included only demographic covariates, described the concentration–time profiles slightly better than model B (which included cardiac output as a covariate). This is in contrast with what we expected, because cardiac output is expected to be a more direct determinant of both the distribution and elimination of lidocaine (which is known to have a flow-limited elimination clearance).[4] There are two possible explanations for this phenomenon. In our study, we used a compartment model for the pharmacokinetic analysis. This is not capable of describing pulmonary uptake. This could be especially relevant for a drug such as lidocaine, which has an initial pulmonary uptake of more then 90%.[28,29] Pulmonary uptake will influence the early blood concentration–time profile of lidocaine, which is used to estimate volume V_1. The estimation of V_1 is also significantly affected by the moment of first sampling after an intravenous bolus injection.[30] The inability of compartmental models to adequately describe the initial distribution kinetics may obscure the role of the cardiac output with respect to the distribution parameters of lidocaine. In this respect, the influence of cardiac output is probably better described by other pharmacokinetic models, such as recirculatory models that can accommodate the initial distribution, including the lung uptake. However, these models do not allow the estimation of population pharmacokinetics.

On the other hand, the models that include cardiac output as a covariate (models B and D) showed a distinct relation between cardiac output and the elimination clearance. This is especially important for lidocaine, because it is usually administered by long-term continuous infusion. In this situation, the ultimately achieved steady state concentration will be inversely proportional to the elimination clearance. If, based on measurements of cardiac output, the elimination clearance could be predicted, the optimal infusion rate to achieve a given steady state concentration could be calculated. This may be particularly important with drugs, such as lidocaine, that have a relatively narrow therapeutic window. In the current study, the performance of the four evaluated models, which included observations during the distribution phase, differed only marginally. However, computer simulations showed that steady state concentrations, predicted by the different models, might differ considerably. In the average patient, concentrations predicted by models B and D indeed appear to be similar (fig. 3). However, according to models C and D, the elimination clearance also depends on body weight, and, therefore, concentrations predicted on the basis of models B and D may differ markedly if a patient's body weight differs considerably from the average. In that model D accommodates both body weight and cardiac output, and therefore is more flexible than the models A, B, and C, and given its better performance after a bolus injection, we are confident that this is the preferred model. However, its performance during continuous infusions remains to be established.

The use of the bioimpedance method for the determination of individual cardiac output measurements can be considered a drawback of our study that might have limited the success of incorporation of cardiac output as a covariate. However, although the use of more accurate methods such as thermodilution would have been preferable, for ethical reasons this option was not used. Studies comparing the thoracic bioimpedance and the thermodilution method have produced varying results. In a large multicenter study, the methods were shown to be reasonably comparable.[7] In that study, the bias of the bioimpedance method compared with the thermodilution method was only −0.013 l/min, and limits of agree-

ment between both methods were −1.41 and +1.39 l/min, respectively.

In conclusion, this study showed that the inclusion of cardiac output, in addition to demographic characteristics, in a population pharmacokinetic model of lidocaine, improved the prediction of the pharmacokinetics of individual patients. However, the improvement was marginal. This may, in part, be a result of the inability of the compartmental model to accommodate the early distribution kinetics. Further improvement may be obtained with more appropriate models, such as a recirculatory model, and more precise measurements of cardiac output.

The authors thank Rene A. G. Mooren, B.Sc., and Wim Olieman, Anesthesia Research Laboratory (Head, Anton G. L. Burm, Ph.D.), Leiden University Medical Center, Leiden, The Netherlands, for the determination of the lidocaine concentrations.

Appendix

Whole-blood lidocaine concentrations were determined using capillary gas chromatography. To 0.5 ml blood samples, 25 μl ethanol (patient samples) or 25 μl ethanol containing standard amounts of lidocaine hydrochloride (5.85–702 ng, calibration samples) and 25 μl ethanol containing 200 ng prilocaine hydrochloride as internal standard (all samples) were added. After mixing, 5 ml n-pentane was added, and the sample was subsequently extracted for 5 min on a whirl mixer. After centrifugation at 3,500 rpm, the organic layer was transferred to a test tube and evaporated to dryness at 40°C under a stream of dry nitrogen. The residue was dissolved in 100 μl ethanol, and 1.6 μl of this solution was injected into the gas chromatograph using a solid injection system (Chrompack, Bergen op Zoom, The Netherlands).

Analyses were conducted with a Hewlett-Packard 5890-series 2 gas chromatograph (Hewlett Packard, Rolling Meadows, IL) equipped with a nitrogen detector and a capillary fused-silica column (length, 12.5 m; ID, 0.32 mm) with Wax 57 CB (Chrompack) as the stationary phase. The operating temperatures of the column–oven, injection port, and detector were 180, 300, and 300°C, respectively. Helium was used as the carrier gas (flow rate, 4.4 ml/min), and an auxiliary flow of helium (13.9 ml/min) was fed into the detector. Chromatograms were analyzed using Chemstation (Hewlett Packard) software. Calibration lines were obtained by weighted ($1/y^2$) least squares regression analysis of the peak height ratio of lidocaine–prilocaine *versus* the concentration of lidocaine.

The retention times of lidocaine and prilocaine were 2.8 and 3.0 min, respectively. Calibration lines (n = 15) were linear in the investigated range (11.7–1404 ng lidocaine per milliliter of blood), with correlation coefficients varying from 0.997 to more than 0.9999. The interday coefficient of variation (n = 15) was 2.4% in the investigated concentration range. The lower limit of detection was 3 ng/ml whole blood.

References

1. Wright PMC: Population based pharmacokinetic analysis: Why do we need it; what is it; and what has it told us about anaesthetics? Br J Anaesth 1998; 80:488–501

2. Runciman WB, Upton RN: Pharmacokinetics and pharmacodynamics: What is of value to the practising anaesthetist? Anaesth Pharmacol Rev 1994; 2:280–93

3. Henthorn TK, Krejcie TC, Avram MJ: The relationship between alfentanil distribution kinetics and cardiac output. Clin Pharmacol Ther 1992; 52:190–6

4. Colli A, Buccino G, Cocciolo M, Parravicini R, Scaltrini G: Disposition of a flow-limited drug (lidocaine) and a metabolic capacity-limited drug (theophylline) in liver cirrhosis. Clin Pharmacol Ther 1988; 44:642–9

5. Haruna M, Kumon K, Yahagi N, Watanabe Y, Ishida Y, Kobayashi N, Aoyagi T: Blood volume measurement at the bedside using ICG pulse spectrophotometry. ANESTHESIOLOGY 1998; 89:1322–8

6. Iijima T, Aoyagi T, Iwao Y, Masuda J, Fuse M, Kobayashi N, Sankawa H: Cardiac output and circulating blood volume analysis by pulse dye-densitometry. J Clin Monit Comput 1997; 13:81–9

7. Shoemaker WC, Wo CCJ, Bishop MH, Appel PL, van de Water JM, Harrington GR, Wang X, Patil RS: Multicenter trial of a new thoracic electrical bioimpedance device for cardiac output estimations. Crit Care Med 1994; 22: 1907–12

8. Guzzi L, Jaffe MB, Orr JA: Clinical evaluation of a new noninvasive method of cardiac output measurement: Preliminary results in CABG patients (abstract). ANESTHESIOLOGY 1998; 89(Suppl 3A):A543.

9. Bréant V, Charpiat B, Sab JM, Maire P, Jelliffe RW: How many patients and blood levels are necessary for population pharmacokinetic analysis? Eur J Clin Pharmacol 1996; 51:283–8

10. Burm AGL, de Boer AG, van Kleef JW, Vermeulen NP, de Leede LG, Spierdijk J, Breimer DD: Pharmacokinetics of lidocaine and bupivacaine and stable isotope labelled analogues: A study in healthy volunteers. Biopharm Drug Dispos 1988; 9:85–95

11. Beal SL, Sheiner LB, Boeckmann A: NONMEM User's Guides. San Francisco, University of California, 1999

12. Varvel JR, Donoho DL, Shafer SL: Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm 1992; 20:63–94

13. Upton RN, Huang YF: Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep. Br J Anaesth 1993; 70:333–8

14. Björkman S, Wada DR, Stanski DR: Application of physiologic models to predict the influence of changes in body composition and blood flows on the pharmacokinetics of fentanyl and alfentanil in patients. ANESTHESIOLOGY 1998; 88:657–67

15. Wada DR, Ward DS: The hybrid model: A new pharmacokinetic model for computer-controlled infusion pumps. IEEE Trans Biomed Eng 1994; 41:134–42

16. Dyck JB, Wallace MS, Lu JQ, Rossi SS, Yaksh TL: The pharmacokinetics of lignocaine in humans during a computer-controlled infusion. Eur J Pain 1997; 1:141–8

17. Rowland M, Thomson PD, Guichard A, Melmon KL: Disposition kinetics of lidocaine in normal subjects. Ann N Y Acad Sci 1971; 179:383–98

18. Benowitz N, Forsyth RP, Melmon KL, Rowland M: Lidocaine disposition kinetics in monkey and man. I. Prediction by a perfusion model. Clin Pharmacol Ther 1974; 16:87–98

19. Vozeh S, Berger M, Wenk M, Ritz R, Follath F: Rapid prediction of individual dosage requirements for lignocaine. Clin Pharmacokinet 1984; 9:354–63

20. Avram MJ, Sanghvi R, Henthorn TK, Krejcie TC, Shanks CA, Fragen RJ, Howard KA, Kaczynski DA: Determinants of thiopental induction dose requirements. Anesth Analg 1993; 76:10–7

21. Wada DR, Björkman S, Ebling WF, Harashima H, Harapat SR, Stanski DR: Computer simulation of the effect of alterations in blood flows and body composition on thiopental pharmacokinetics in humans. ANESTHESIOLOGY 1997; 87: 884–99

22. Ben-Sira D, Sagiv M: The effect of gender on left ventricular function immediately after the wingate test. Eur J Appl Physiol 1997; 75:549–53

23. Proctor DN, Beck KC, Shen PH, Eickhoff TJ, Halliwill JR, Joyner MJ: Influence of age and gender on cardiac output-VO_2 relationships during submaximal cycle ergometry. J Appl Physiol 1998; 84:599–605

24. Brandfonbrener M, Landowne M, Shock NW: Changes in cardiac output with age. Circulation 1955; 12:557–66

25. Kuikka JT, Länsimies E: Effect of age on cadiac index, stroke index and left ventricular ejection fraction at rest and during exercise as studied by radiocardiography. Acta Physiol Scand 1982; 114:339–43

26. Rodeheffer RJ, Gerstenblith G, Becker LC, Fleg JL, Weisfeldt ML, Lakatta EG: Exercise cardiac output is maintained with advancing age in healthy human subjects: Cardiac dilatation and increased stroke volume compensate for a diminished heart rate. Circulation 1984; 69:203–13

27. Tsujimoto G, Hashimoto K, Hoffman BB: Pharmacokinetic and pharmacodynamic principles of drug therapy in old age. Part I. Int J Clin Pharmacol Ther Toxicol 1989; 27:13–26

28. Jorfeldt L, Lewis DH, Löfström JB, Post C: Lung uptake of lidocaine in healthy volunteers. Acta Anaesthesiol Scand 1979; 23:567–74

29. Jorfeldt L, Lewis DH, Löfström JB, Post C: Lung uptake of lidocaine in man as influenced by anaesthesia, mepivacaine infusion or lung insufficiency. Acta Anaesthesiol Scand 1983; 27:5–9

30. Chiou WL: Potential pitfalls in the conventional pharmacokinetic studies: Effects of the initial mixing of drug in blood and the pulmonary first-pass elimination. J Pharmacokinet Biopharm 1979; 7:527–36