

A Population Model of Epidural Lidocaine – Effects of Dopamine

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Abstract **OBJECTIVE** - To examine the population behavior of epidural lidocaine in geriatric patients, and to search for any difference in the PK behavior of epidural lidocaine when dopamine is given concurrently.

METHODS - Twenty patients over age 65, undergoing peripheral vascular surgery under continuous lidocaine epidural anesthesia, were studied. Ten received an intravenous (IV) infusion of placebo (normal saline), while ten other patients received an IV infusion of dopamine at 2 mg/kg/min. Total arterial plasma lidocaine concentrations (GLC assay) were measured 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 (NPAG) computer program in the MM-USC*PACK collection was utilized for population PK modeling to obtain the entire discrete maximum likelihood joint parameter distribution [1-3]. 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 ($Ka \text{ part} + K2-0$) from the epidural space to the serum compartment, and this rate was slowed, by about 40%, probably significantly, by dopamine. The rate constant of elimination from the serum compartment ($K2-0$) was somewhat increased by dopamine. The rate constant for drug movement from central to peripheral compartment ($K2-3$) was also somewhat increased in the dopamine patients. The rate constant back from the peripheral to the central compartment ($K3-2$) was somewhat slowed by dopamine. There was no obvious difference in the apparent volume of distribution of the central compartment between the placebo and the dopamine patients.

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				
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				
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				
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				
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				
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

CONCLUSIONS - In this first population model of epidural lidocaine, to our knowledge, low-dose dopamine appears to decrease the rate of transfer of lidocaine from the epidural to the serum compartment, and also to increase both the rate of elimination of lidocaine and 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 infusion rates) were also similar for the two groups, though they were slightly less for the dopamine patients, consistent with the slower removal of lidocaine from the epidural compartment. This model may be useful in the future to design more optimal epidural infusion protocols.

REFERENCES - [1] Schumitzky A. Nonparametric EM algorithms for estimating prior distributions. *App. Math Computation* 1991;45:143-57.

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[3] Bustad A, Terziivanov D, Leary R, Port R, Schumitzky A, and Jelliffe R: Parametric and Nonparametric Population Methods: Their Comparative Performance in Analysing a Clinical Data Set and Two Monte Carlo Simulation Studies. *Clin. Pharmacokinet.* 45: 365-383, 2006.

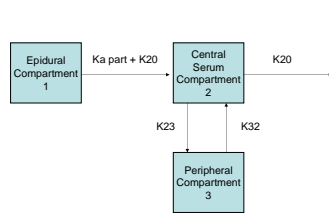


Figure 1. The structural model of lidocaine kinetics. Compartment 1 represents the epidural compartment into which lidocaine was injected and infused. Compartment 2 represents the serum concentration compartment. Compartment 3 represents the peripheral (nonserum) compartment. Model parameters are ($Ka \text{ part} + K20$) for absorption from the epidural into the serum concentration compartment (always greater than $K20$, the elimination rate constant from the central compartment). $K23$ represents the rate constant from the central to the peripheral compartment, $K32$, the rate constant back from the peripheral compartment, and $V2$, the apparent volume of distribution of the central compartment.

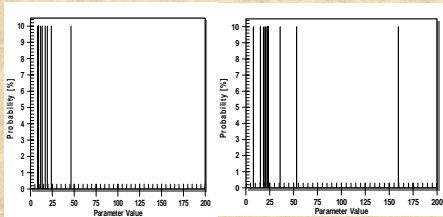


Figure 2a. Marginal density plot of the parameter Ka part. Placebo patients.

Figure 2b. Marginal density plot of the parameter Ka part. Dopamine patients. Note the lower parameter values here than in Figure 2a.

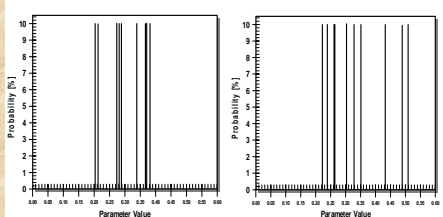


Figure 3a. Marginal density plot of the parameter K2-0. Placebo patients.

Figure 3b. Marginal density plot of the parameter K2-0. Dopamine patients.

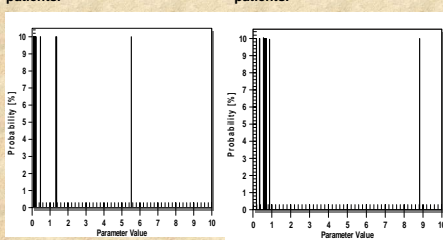


Figure 4a. Marginal density plot of the parameter K2-3. Placebo patients.

Figure 4b. Marginal density plot of the parameter K2-3. Dopamine patients.

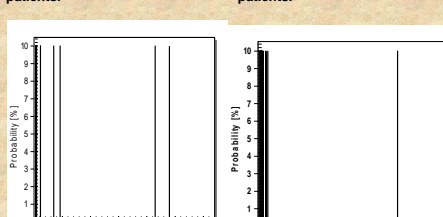


Figure 5a. Marginal density plot of the parameter K3-2. Placebo patients.

Figure 5b. Marginal density plot of the parameter K3-2. Dopamine patients.

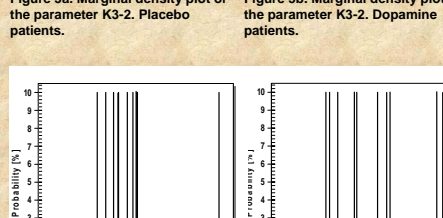


Figure 6a. Marginal density plot of the parameter V2. Placebo patients.

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

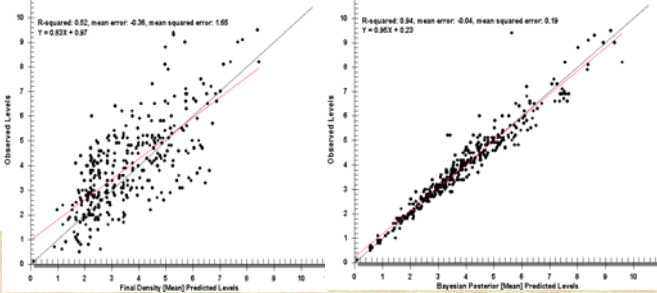


Figure 7a. Scatterplot of estimated versus measured serum concentrations, based on medians of population parameter distributions. Pooled data of all patients.

Figure 7b. Scatterplot of estimated versus measured serum concentrations, based on medians of individual subject Bayesian posterior parameter distributions. Pooled data of all patients.

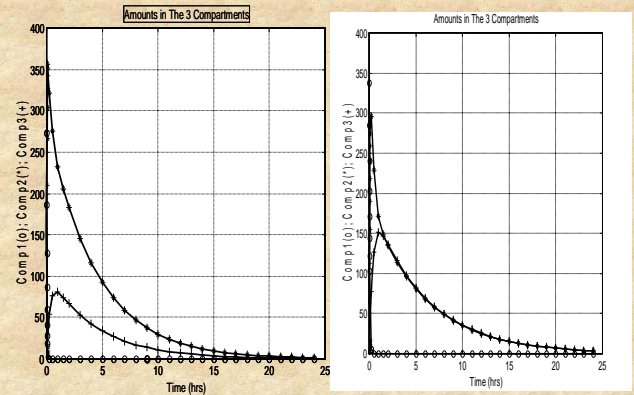


Figure 8a, left. Placebo patients. Mean parameter values. Amounts of drug in epidural compartment 1 (bottom), serum compartment 2 (top), and peripheral compartment 3 (middle) simulated from a 400 mg epidural bolus into epidural compartment 1 at time 0. Time from 0 to 24 hours.

Figure 8b, right. Dopamine patients. Same simulation. See text for discussion.

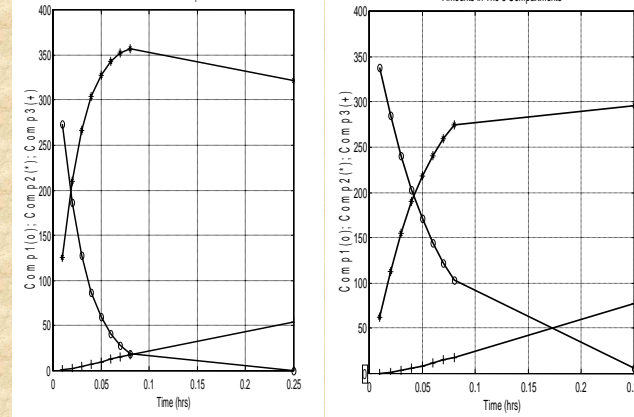


Figure 9a, left. Same as Figure 8a, but only showing events during the first 15 minutes (0.25hr).

Figure 9b, right. Same as Figure 8b, but only showing events during the first 15 minutes (0.25hr).

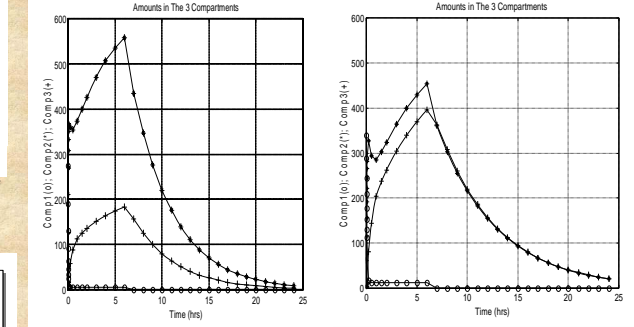


Figure 10a, left. Placebo patients, mean parameter values. Simulation of results from an epidural bolus of 400 at time 0.0, followed by an epidural infusion of 200 mg/hour for 6 hours. Again, epidural amounts in compartment 1 (bottom), amounts in serum compartment 2 (top), and amounts in peripheral compartment 3 (middle).

Figure 10b, right. Dopamine patients, mean parameter values. Simulated results of the same bolus followed by the same infusion for 6 hours. Amounts in epidural compartment 1 (bottom), serum compartment 2 (top), and amounts in the peripheral compartment 3 (middle).