Improvement of local anesthetics agents' simulation using Monte Carlo simulation considering correlation among parameters

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Abstract

Animal experiments using guinea pigs are performed to elucidate the effects of local anesthetic agents. Simulators are used in various fields as an animal alternative. Herein, we aimed to develop a simulator for local anesthetic agents. In a previous study, we developed a statistical model to simulate the effects of local anesthetic agents. We estimated the parameters of the distribution (mean [μ] and logarithm of standard deviation [$\log\sigma$]) for each drug based on the results of animal experiments. We reported that Monte Carlo simulation yielded results consistent with those from the animal experiments. However, since this simulation did not account for parameter correlation, we observed a large variation in drug parameter values within individual subjects. This led to the order of drug duration being different from the original order in many individuals. In the present study, we investigated correlations among these parameter values, performed simulations using parameter values that followed a multivariate normal distribution, and examined the correlation of duration among drugs to address these shortcomings. Correlation coefficients between μ and $\log\sigma$ ($r_{\mu-\log\sigma}$) were -0.4 to 0.01. Correlation coefficients for μ (r_{μ}) and $\log\sigma$ ($r_{\log\sigma}$) were 0.4 to 0.6, and 0.3 to 0.6, respectively. In Monte Carlo simulation, when $r_{\mu-\log\sigma}$ was small, the standard deviation of duration within one drug was large. Moreover, when r_{μ} and $r_{\log\sigma}$ were large, the correlation of duration between two drugs was large. When correlation among parameters was not set, the correlation coefficient for duration was small (-0.12 to 0.26), but when these were set to parameter values obtained from animal experiments, the correlation coefficient for duration became large (0.22 to 0.47). These findings suggest that by considering the correlation among parameters it is possible to create a simulator for local anesthetic agents that obtains the results closer to those of animal experiments.

Keywords: local anesthetics, Monte Carlo simulation, correlation coefficient

1 Introduction

Local anesthetic agents are used to eliminate pain during surgery. Understanding the relationship between the properties of local anesthetic agents and their effects is clinically important. Local anesthetic agents pass through the cell membrane, block the voltage-gated sodium channels from within the cell, and suppress nerve conduction [1, 2]. The important factors that determine the action of local anesthetic agents include the drug's lipid solubility, protein-binding ability, vasodilator effect, and the presence of vasoconstrictor agents [1, 2]. We have been conducting animal experiments in pharmacology training to elucidate these factors. We conducted an experiment to compare and examine the effects of local anesthetic agents by subcutaneously injecting several types of local anesthetic agents into the backs of guinea pigs and measuring the number of reactions when stimulated with a needle.

As animal welfare becomes increasingly important, a corresponding decrease in the number of animals used for experiments is desirable. In identifying animal use alternatives, the 3Rs are an effective strategy: Replacement (directly replace or avoid the use of animals), Reduction (obtain comparable information levels from fewer animals), and Refinement (minimize or eliminate animals' pain and distress, improving their welfare) [3]. Computer simulations surve as alternatives to animal testing in various areas including pharmacokinetics [4, 5], organ bath systems, and cardiovascular systems (such as Strathclyde Pharmacology Simulations package: OBSim, RatCVS and Virtual Cat) [6]. While there are numerous commercially available simulators for technical training related to local anesthetics agents, to our knowledge, none specifically target pharmacological effects such as intensity or duration of drug effects. We aimed to develop a simulator for this purpose.

We first set up a model equation using a hierarchical Bayesian model to estimate the effects of local anesthetic agents based on the results obtained in animal experiments, and estimated parameter values [7].

Results were obtained by generating random numbers according to parameter values in simulation. This method is called Monte Carlo simulation. In pharmacology, Monte Carlo simulation has primarily been used for pharmacokinetic/pharmacodynamic (PK/PD) modeling techniques, especially in population pharmacokinetics, to optimize clinical outcomes through rational dosing strategies [8]. Previous studies have reported its application for antibacterial drugs [9–11], antiviral drugs [12–14], anticancer drugs [15], and opioids [16]. Moreover, there are several studies about local anesthetic agents for population pharmacokinetics to determine the maximum recommended dose regimen [17] and for the confirmation of the molecular mechanism of the Na channel [18, 19].

In our previous study [7], we adjusted parameter values based on the estimated values obtained, generated random numbers according to the parameter values, and performed Monte Carlo simulations to examine whether the same results as animal experiments could be obtained. We obtained similar results to animal experiments. However, the simulation did not consider the correlation between the durations of each drug, and the parameter values were generated by random numbers with the correlation coefficients between drugs set to zero. Therefore, even when offset values were included in the model to account for individual differences, there were both drugs with values

greater than the mean value and drugs with values less than the mean value within one individual. Thus, the magnitude relationship of the parameter values (μ_0) was reversed between procaine (Pro) and lidocaine (Lid), which have close parameter values, and there were many individuals whose duration was opposite to the original one. However, individuals who tend to respond to one drug are likely to respond to other drugs as well in clinical practice. Therefore, the duration of each drug is also correlated, and it is desirable to consider this correlation when creating a simulator.

In this study, we investigated the correlation between parameter values (μ, $\log \sigma$) that determine the distribution of each drug. We performed a simulation using parameter values that considered the correlation among drugs by generating random numbers that followed a multivariate normal distribution, and examined the correlation in duration among drugs. Moreover, we examined the effect of correlation coefficient of the parameter values (μ and $\log \sigma$) on the duration correlation. We aimed to create a simulator for local anesthetic agents that will yield results closer to those of animal experiments.

2 Materials and Methods

2.1 Animal experiments

In this study, we used the drug parameter values estimated by Hierarchical Bayesian models and Hamiltonian Monte Carlo simulation as reported in our previous study [7]. The data is available on Zenodo (param1.csv and param1_individual.csv in `https://doi.org/10.5281/zenodo.10775798`).

The animal experiment method was reproduced as follows: (1) shave the hair on the back of the guinea pig; (2) 0.1 ml of saline and five drugs, consisting of 1% procaine hydrochloride (Pro), 1% lidocaine hydrochloride (Lid), 1% mepivacaine hydrochloride (Mep), 1% bupivacaine hydrochloride (Bup), and 1% lidocaine hydrochloride with 1/100,000 adrenaline (Lid + Adr), are injected intradermally; (3) each papule was stimulated with a needle six times and the number of the skin contractions was counted (this number was defined as the score ranging between 0 and 6[maximum]); (4) stimulate at 5 min intervals up to 100 min. When a score of 6 was obtained three times in a row, the stimulation was finished, and that time was defined as the duration.

All results from 2019, 2021 and 2022 were used (total number of animals was 51). This experiment was approved by the Animal Management Committee of Matsumoto Dental University (No. 356 in 2019, No. 396 in 2021, and No. 413 in 2022).

2.2 Computer simulation

2.2.1 Software and programs used

We used R (version 4.3.3) [20] for data analysis. A random number seed value was set to ensure the reproducibility of the simulation. In this study, parameter values and score values were determined using multiple seed values. The programs used in this study are available on Zenodo (`https://doi.org/10.5281/zenodo.10905849`).

2.2.2 Parameters of drugs

The values estimated by model 1 (param1.csv) of the previous study [7] were used as references for the parameter values of each drug when performing the simulation. This model does not consider individual differences (offset values). According to these parameter values, we generated random numbers following an 8-variate standard normal distribution by equations 1 and 2, and set the values of mean (μ) and logarithmic standard deviation (SD) ($\log\sigma$) in each drug and individual by equations 3 and 4, respectively. Random numbers following a multivariate normal distribution were generated using the rmvrorm function of the mvtnorm library [21] in R. The conditions were as follows:

$$\Sigma = \begin{pmatrix} 1 & r_{12} & r_{13} & r_{14} & u_1 & 0 & 0 & 0 \\ r_{12} & 1 & r_{23} & r_{24} & 0 & u_2 & 0 & 0 \\ r_{13} & r_{23} & 1 & r_{34} & 0 & 0 & u_3 & 0 \\ r_{14} & r_{24} & r_{34} & 1 & 0 & 0 & 0 & u_4 \\ u_1 & 0 & 0 & 0 & 1 & s_{12} & s_{13} & s_{14} \\ 0 & u_2 & 0 & 0 & s_{12} & 1 & s_{23} & s_{24} \\ 0 & 0 & u_3 & 0 & s_{13} & s_{23} & 1 & s_{34} \\ 0 & 0 & 0 & u_4 & s_{14} & s_{24} & s_{34} & 1 \end{pmatrix} \tag{1}$$

$$X[k,j] \sim N_8(\mathbf{0}, \Sigma) \tag{2}$$

$$\mu[i,j] = \mu_0[i] + s_{\mu_0}[i]\, X[i,j] \tag{3}$$

$$\log\sigma[i,j] = \log\sigma_0[i] + \log s_{\sigma_0}[i]\, X[i+4,j] \tag{4}$$

where

Σ is the variance-covariance matrix

r is the correlation coefficient of μ among drugs (r_μ)

s is the correlation coefficient of $\log\sigma$ among drugs ($r_{\log\sigma}$)

u is the correlation coefficient between μ and $\log\sigma$ in each drug ($r_{\mu-\log\sigma}$)

X are random numbers following an 8-variate standard normal distribution

$i = 1, 2, 3, 4$ (1: Pro, 2: Lid, 3: Mep, 4: Bup)

$j = 1, 2, \cdots, n$ (individuals)

$k = 1, 2, \cdots, 8$ (1, 5: Pro; 2, 6: Lid; 3, 7: Mep; 4, 8: Bup)

$\mu[i,j]$ is the mean of distribution in each drug and individual

$\mu_0[i]$ and $s_{\mu_0}[i]$ are mean and SD of $\mu[i,j]$ in each drug

$\log\sigma[i,j]$ is the SD of distribution in each drug and individual

$\log\sigma_0[i]$ and $\log s_{\sigma_0}[i]$ are mean and SD of $\log\sigma[i,j]$ in each drug

2.2.3 Probability prediction curve, score value, and duration

The probability p that responds to a stimulus at time t was calculated using equation 5 [7]. The sigmoid curve obtained by this equation was used as the probability prediction curve.

$$p = 1 - \Phi\left(\frac{100 - (1 - 0.7 \times V_{\mathrm{adr}})\, t - \mu[i,j]}{\sigma[i,j]}\right) \tag{5}$$

where

Φ is the cumulative normal distribution function
$\mu[i,j]$ and $\sigma[i,j]$ are the mean and SD of drug in each individual, respectively
V_{adr} is the dummy variable
(0 when adrenaline is absent, 1 when adrenaline is present)
t is time after administration (min)

The probability was determined every 5 minutes from the start of the simulation, and random numbers were generated according to the binomial distribution based on the probability (trial = 6). The obtained value was used as the score value. When a score value of 6 occurred three times in a row, the third time was taken as the duration of the drug.

2.2.4 Comparison of local anesthetic agent duration between animal and simulation data

Comparison of drug duration between each condition was performed using survival analysis. Results up to 100 minutes were used in animal experiments and up to 180 minutes in simulations. Anything longer than that was treated as censored data. The analysis was performed using the survfit function of the survival package [22] in R.

2.2.5 Mixed linear model

We investigated whether the influence of the value of r_μ on the correlation of drug duration differs depending on the value of $r_{\log\sigma}$ using a linear mixed model. The objective variable is the correlation coefficient of duration; the fixed effect is r_μ, $r_{\log\sigma}$ and their interaction; and the random effect is a random seed value (categorical variable). Analysis was performed using a random intercept model using the lmer function of the lmerTest package [23], which extends the functionality of the lme4 package [24] in R.

3 Results

3.1 Correlation of parameter values of each drug in animal experiments

We examined the correlation between the parameter values of μ and $\log\sigma$ estimated by model 1 in animal experiments [7] for each drug. Since we assumed that σ follows a lognormal distribution (that is, $\log\sigma$ follows a normal distribution), we used $\log\sigma$ as a parameter in this study. We identified an individual who was be an outlier in Pro (Figure 1A). Pearson's correlation coefficient between μ and $\log\sigma$ ($r_{\mu-\log\sigma}$) were -0.42 to 0.01, which were a negative correlation to no correlation (Table 1).

We created a probability prediction curve using the parameter values for each individual (Figure 1B). In Pro, only one curve was different from the others. Bup had large variations in the horizontal position of the curve and the slope of the curve (Figure 1B).

3.2 Correlation of parameter values among drugs in animal experiments

We compared parameter values (μ and $\log\sigma$) estimated from data obtained in animal experiments among different drugs. Given the valiability in mean values and SDs among these drugs, we calculated a standardized value (normal score) for each parameter. When we created parallel coordinates to examine the relationship of parameters among drugs, a tendency for the normal scores of all drugs to be large or small within the same individual was observed, although there was some variation (Figure 2A). These results suggest that there was a positive correlation of parameters among drugs in μ and $\log\sigma$.

When examining the correlation of parameter values among drugs, we observed positive correlations in μ (Figure 2B) and $\log\sigma$ (Figure 2C). Figure 2B shows two values that were outliers from the group. Therefore, we considered individuals with an absolute normal score value of 2 or more as outliers. Table 2 shows the correlation coefficients after excluding outliers. After excluding outliers, r_μ was about 0.4 to 0.6, and $r_{\log\sigma}$ was about 0.3 to 0.6, indicating very weak to weak correlations. In addition, $r_{\mu-\log\sigma}$ went from -0.31 to 0.01, and the correlation became weaker than before the exclusion (Table 1).

The results of comparing the duration of each drug are shown in Figure 2D. There was a positive correlation in duration among all drugs. Due to the presence of censored data, it was inappropriate to calculate Pearson's correlation coefficient. Therefore, we calculated Spearman's rank correlation coefficient. Spearman's rank correlation coefficient was about 0.39 to 0.59 before excluding outliers, and about 0.38 to 0.60 after excluding outliers (Supplemental Table 1). These results suggest that there was positive correlation of duration among drugs.

3.3 Effect of correlation of drug parameter values ($r_{\mu-\log\sigma}$) in simulation experiments

We examined the duration of each drug by Monte Carlo simulation. Drug parameter values (μ_0, s_{μ_0}, $\log\sigma_0$, and $s_{\log\sigma_0}$) were set based on the values of our previous study [7] (Table 3). First, we investigated the influence of $r_{\mu-\log\sigma}$ on the shape of the probability prediction curve using parameter values of Lid. In this simulation, the correlation coefficients among drugs (r_μ and $r_{\log\sigma}$) were set to 0. We generated 100 sets of parameter values for each $r_{\mu-\log\sigma}$ using random numbers, and created a probability prediction curve. Out of the results obtained by parameter values generated using multiple seed values, the data for one seed value is shown (Figure 3A). When the value of $r_{\mu-\log\sigma}$ is small, the range of the curve is narrow in the region where the predicted probability is small, and the range of the curve is wide in the region where the predicted probability is large. On the other hand, when the value of $r_{\mu-\log\sigma}$ is large, the range of the curve is

wide in the region where the predicted probability is small, and the range of the curve is narrow in the region where the predicted probability is large.

Next, score values were obtained by simulation using the generated parameter values, and the durations of drug were calculated. For each $r_{\mu-\log\sigma}$, the mean value and SD of 100 sets of durations were calculated. The mean duration was almost constant regardless of $r_{\mu-\log\sigma}$ (Figure 3B), but the SD decreased as $r_{\mu-\log\sigma}$ increased (Figure 3C). These results are consistent with the results in Figure 3A. The results of simulations performed under multiple conditions are shown in Supplemental Figure 1.

3.4 Effect of correlation of drug parameter values (r_μ and $r_{\log\sigma}$) on genereted parameters

We examined the influence of r_μ and $r_{\log\sigma}$ on the correlation of duration using Pro and Lid as representatives. Since both r_μ and $r_{\log\sigma}$ showed positive values (Figure 2 and Table 2), we set the values of r_μ and $r_{\log\sigma}$ between Pro and Lid to be from 0 to 1, and obtained the duration by simulation. In this simulation, $r_{\mu-\log\sigma}$ value was set to 0. For each combination of r_μ and $r_{\log\sigma}$ values, we generated 100 sets of parameter values and then calculated the duration of Pro and Lid. As the value of r_μ and/or $r_{\log\sigma}$ increases, the correlation between durations increases (Figure 4A). The influence of r_μ and $r_{\log\sigma}$ was about the same under the present conditions (Figure 4B). The results of simulations performed under multiple conditions are shown in Supplemental Figure 2.

Next, we examined whether the influence of the value of r_μ on the duration correlation differs depending on the value of $r_{\log\sigma}$. From the analysis results of a mixed linear model considering the interaction of r_μ and $r_{\log\sigma}$, we found that the influence of the value of r_μ did not differ depending on the value of $r_{\log\sigma}$ (term of interaction: $t = 0.973$, degree of freedom = 277, $P = 0.331$) (Supplemental Table 2).

3.5 Effect of correlation of drug parameter values ($r_{\mu-\log\sigma}$, r_μ and $r_{\log\sigma}$) on duration

Using parameter values estimated from the results of animal experiments, we examined the correlation of duration among each drug. The parameter value settings are shown in Tables 3 and 4. We used the parameter values shown in Table 3, but r_μ was set to 0 in Condition 1 and Condition 3, and$r_{\log\sigma}$ was set to 0 in Condition 1 and Condition 2. After generating 100 sets of parameter values under each condition, a simulation was performed and the correlation coefficients of duration among drugs were calculated (Figure 5 and Table 4). Similar to the results in Figure 4, when r_μ and $r_{\log\sigma}$ are set (Condition 1 and Condition 3), the correlation coefficient of duration among drugs increases (Table 4). On the other hand, even when $r_{\mu-\log\sigma}$ is set, the correlation coefficients of duration are almost the same (Condition 1 vs. Condition 2, and Condition 3 vs. Condition 4), indicating that the influence of $r_{\mu-\log\sigma}$ was small (Table 4). Spearman's rank correlation coefficients are shown in Supplemental Table 3 and the results of simulations performed under multiple conditions are shown in Supplemental Figure 3.

Next, we compared the duration of the animal experiment and the simulation. When the median duration and 95% confidence interval of each drug were compared among

conditions, the simulation results for Pro, Lid, and Mep showed values close to the animal experiment results (Table 5). On the other hand, although it was not possible to determine the median value for Bup in animal experiments, the simulation results showed almost the same value under all conditions (Table 5). The Kaplan-Meier plots under multiple conditions are shown in Supplemental Figure 4.

In general, the duration of Lid was longer than that of Pro. However, in both animal experiments and simulations, many individuals exhibited a longer duration for Pro compared to Lid. Therefore, we investigated the rate at which numerical reversals were observed in parameter values and durations (Table 6). Among the 51 cases of animal experiments, the cases of Pro $>$ Lid in μ value, which is the original relationship, was 31 (61and Pro $<$ Lid was 20 (39In the simulation results, the rate of Pro $<$ Lid was about 30but about 20(Table 6). These results suggest that the probability of Pro $<$ Lid decreases by considering the correlation among drugs. Similarly, when comparing the relationship in duration, out of 51 animal experiments, 29 cases (57six cases (12and 15 cases were Pro $>$ Lid (29One case (2because both cases were not completed within the time limit (Column of Raw data in Table 6). In the simulation results, the rate of Pro $>$ Lid was approximately 3019and 30(Table 6). These results indicate that the rate of Pro $>$ Lid in duration decreases by considering the correlation among drugs.

4 Discussion

In this study, we conducted a Monte Carlo simulation that considered the correlation of parameter values among drugs to examine the correlation in duration among drugs within the same individual. Our findings demonstrated that the correlation of parameter values is important.

4.1 The model used in this study

When estimating parameter values in our previous study [7], we used two models: model 1, which does not consider individual differences, and model 2, which considers offset values as parameter values that indicate individual differences [7]. The parameter values for each individual were almost the same in both models, but the SD of the mean value for each drug (s_{μ_0}) was smaller in model 2. Therefore, we utilized model 2 in subsequent simulations [7].

In this study, we aimed to establish a correlation between parameters instead of using an offset value. When generating parameter values, the variation in parameter values (μ) among individuals in model 1 only reflects the inherent variation in generating these values. On the other hand, model2 incorporates an additional variation in offset values. As a result, the correlation coefficients among parameters in model 1 closely align with the specified variance-covariance matrix. However, in model2, the correlation coefficients of the generated parameters tend to deviate from the assumed values due to the influence of variations in offset values. Based on these observations, we found model 1 to be preferable and utilized it in this study. Therefore, our findings suggest that model 1 is more suitable fro developing a simulator.

4.2 About parameters of drugs

First, we will discuss the relationship between parameter values, the shape of the probability curve, and drug duration. According to equation 5, when the value of μ is small, the probability curve shifts parallel to the right. On the other hand, when the value of $\log\sigma$ is large, the slope of the probability curve becomes small. Since the duration of the drug exists in a time period where the probability is close to 1, the duration becomes longer in small μ and large $\log\sigma$.

Next, we will discuss the effects of $r_{\mu-\log\sigma}$, r_{μ}, and $r_{\log\sigma}$ on the duration.

4.2.1 Relationship between duration and $r_{\mu-\log\sigma}$

The values of $r_{\mu-\log\sigma}$ affect the shape of the probability prediction curve within one drug. When $r_{\mu-\log\sigma}$ is positive, both μ and $\log\sigma$ become large or both become small. Therefore, the curve moves in parallel to the left and the slope becomes small, or the curve moves to the right and the slope becomes large, resulting that the variation of duration and its SD becoming small (Figure 3C). On the other hand, when $r_{\mu-\log\sigma}$ is negative, the curve moves to the left and the slope becomes large, or the curve moves to the right and the slope becomes small, resulting that the variation of duration and its SD becoming large (Figure 3C). The results of animal experiments showed that the values of $r_{\mu-\log\sigma}$ were negative, even when two outliers were excluded, indicating a weak negative correlation to no correlation (Table 1). However, since $r_{\mu-\log\sigma}$ was small (approximately -0.3 in Lid), the effect on the duration is considered to be small.

In addition, the correlation coefficient of the generated parameter values was smaller than the set correlation coefficient (r_{μ}) for the simulation (Tables 2 and 4). It is thought that by generating score values using random numbers, the variation in duration becomes even greater, resulting in the correlation coefficient of duration among drugs becoming smaller.

4.2.2 Relationship between duration and parameters (r_{μ} and $r_{\log\sigma}$)

The values of r_{μ} and $r_{\log\sigma}$ do not impact a single drug's duration individually, but they do influence the correlation of duration between two drugs. As μ and $\log\sigma$ directly influence the duration, larger values of r_{μ} and $r_{\log\sigma}$ result in either a longer or shorter duration for both drugs in each individual (Figure 4). This leads to a higher correlation coefficient for duration. In the results of the animal experiments, positive correlations were observed in parameters (Table 2) and in duration (Supplemental Table 1) among the drugs. These findings indicate consistent variations in duration between drugs within individual subjects.

4.2.3 Significance of setting the correlation coefficient between parameters

The correlation coefficient of duration becomes larger by setting r_{μ} and $r_{\log\sigma}$ (Condition 1 vs. Condition 3 in Figure 5 and Table 4). The simulation in the previous study [7] was performed under Condition 1, which did not consider the correlation of parameter values among drugs. Therefore, the correlation coefficient of duration was less than 0.2, indicating that no correlation was observed. If a simulator is created under

this condition, there will be large variations in the duration among drugs within one individual. On the other hand, in Condition 3 and Condition 4, which considered the correlation of parameter values between drugs, the correlation coefficients of duration were smaller than those of parameter values. Therefore, by appropriately setting the correlation among parameters, results similar to those of animal experiments are obtained, making it possible to create a more appropriate simulator. However, since the absolute value of $r_{\mu-\log\sigma}$ is small (maximum -0.3) (Table 1), $r_{\mu-\log\sigma}$ may have little effect on the duration. We found similar correlation coefficients for Condition 3 and Condition 4 (Table 5), suggesting that setting $r_{\mu-\log\sigma}$ is not essential.

Another advantage is that considering the correlation among parameters increases the rate of obtaining results in the expected order of duration (Table 6). In general, Lid has a longer duration of action than Pro. Therefore, the parameter value of μ is larger for Pro than for Lid. In both Condition 1 and Condition 2, the rates at which the parameter value would be Pro $<$ Lid and the duration would be Pro $>$ Lid were about 30(Table 6). On the other hand, in Condition 3 and Condition 4, the rate of obtaining a reversal in parameter values and duration decreased to about 20These findings are consistent with the results shown in Figure 4. These results underscore the importance of considering the correlation of parameter values. The results of animal experiments showed a higher rate of outcomes contrary to the original expectations compared to the simulations (Table 6). In the animal experiments, the expected duration may not have been achieved due to significant variations in score values iresulting from technical errors. Therefore, the rate at which such contradictory results were obtained may be smaller than that observed in this study.

4.3 Limitations of this study

This study had several limitations. (1) Since this study used the results of animal experiments, it included abnormal data due to failures in experimental procedures such as drug administration, and uneven stimulation strength. Therefore, we calculated correlation coefficients without two outliers based on the standardized score values. Nevertheless, there appears to be substantial variation among drugs (Figure 2A). (2) Since the observation time was limited to 100 minutes in animal experiments, there was many censored data. Therefore, it was not possible to calculate Peason's correlation coefficient of duration in animal experiments. Although it is possible to compare correlations by Spearman's rank correlation coefficients, there is less information on the strength of the correlation compared to Pearson's correlation coefficient. (3) In this study, parameter values were set based on the results of animal experiments. Therefore, as described in the previous study [7], new animal experiments are required to perform simulations under new conditions (drugs and/or concentrations).

4.4 Correlation among parameters in other studies

As an example of research using Monte Carlo simulation, we will consider estimation of blood concentration using a compartment model. A compartment model assumes multiple compartments and differential equations that reflect drug migration among these compartments [1, 25, 26]. Thereafter, we estimated the parameter values from

blood concentration-time data by solving these equations. Moreover, changes in blood concentration are predicted by these equations using estimated parameter values. The main parameter values in the compartment model of pharmacokinetics are absorption rate constant (k_a), volume of distribution (Vd), clearance (CL), and elimination rate constant (k_{12} and k_{21}). Here, it is expected that some correlation exists among the estimated parameter values. However, a previous study [1] only presented mean values (and SDs) without indicating the correlation between each parameter value. Similarly, earlier studies utilizing Monte Carlo simulations [9–14] also neglected to account for the correlation among these parameters. If a correlation exists among the parameters (such as $r_{\mu-\log\sigma}$ in this study), considering this correlation may reduce the rate of generation rare parameter combinations. This could lead to results that are more reflective of reality.

This method described in this study is important when conducting simulations and/or developing simulators. This method can be adapted for to other simulations as well. It is advisable to take into account the correlation among parameters in future studies.

5 Conclusion

In this study, we calculated the correlation coefficients of drug parameter values based on the results of animal experiments. By accounting for the correlation among drugs, the correlation in duration among drugs was enhanced in the simulation, resulting in outcomes more closely aligned with animal experiments. This approach enables the development of a more accurate simulator. When designing simulators for other fields, it is crucial to consider the correlation of parameter values within individuals.

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7 Conflict of Interest

The authors declare that they have no competing interest.

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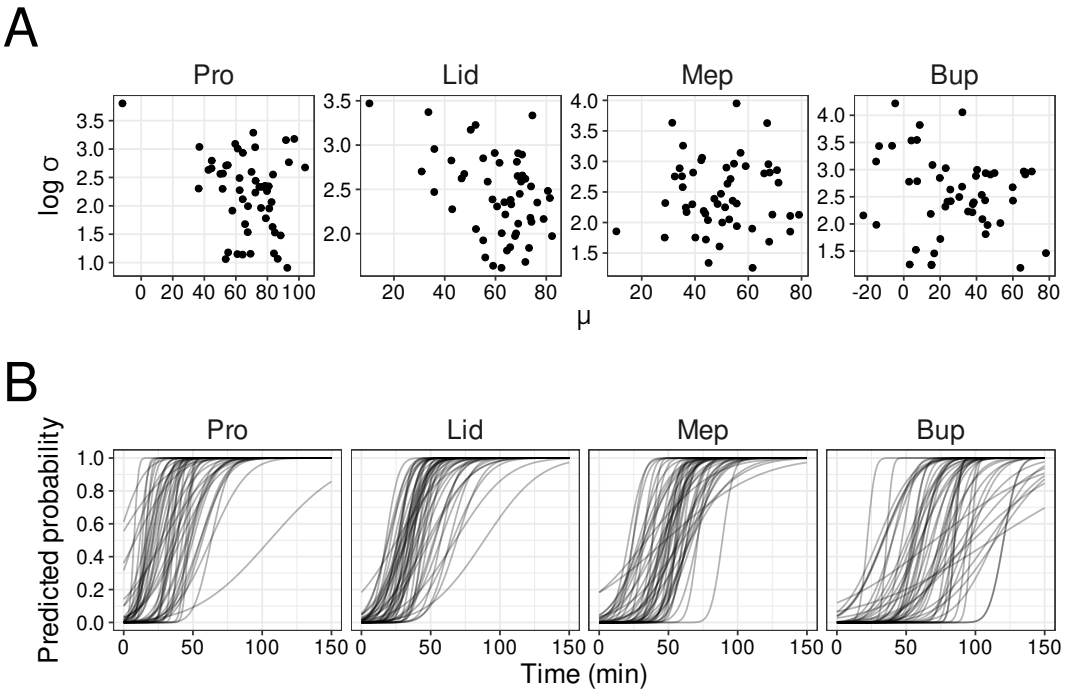

Figure 1: Correlation of parameters between μ and $\log \sigma$ in animal experiments. (A) scatter plot of μ and $\log \sigma$ in each drug, and (B) Predicted probability curve in each drug and individual.

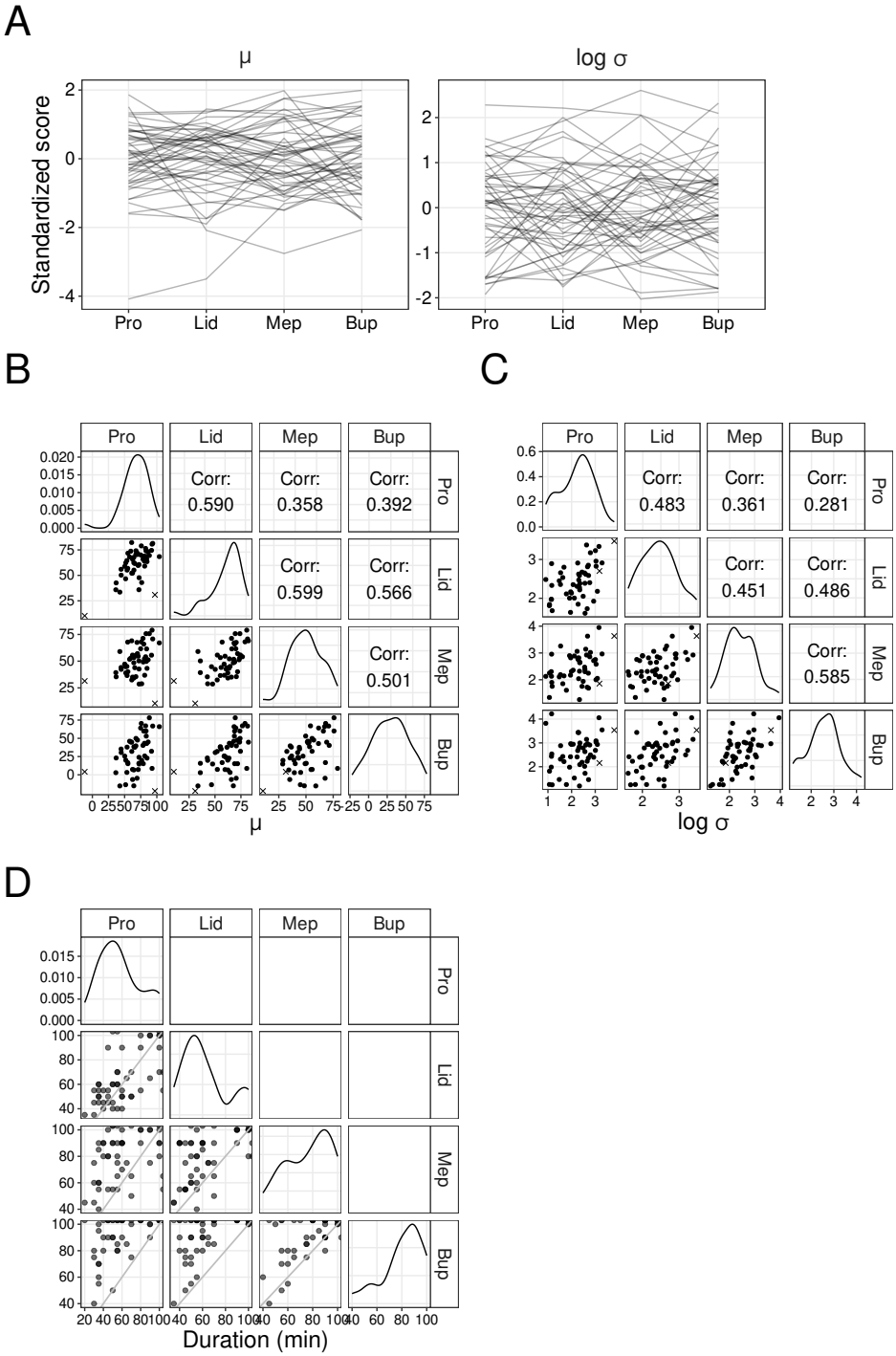

Figure 2: Correlation of parameters and duration among drugs in animal experiments. (A) Parallel coodinates of standarized score of parameters (μ and $\log \sigma$). Each line indicates the data of each individual. (B, C) Scatter plot and Pearson's correlation coefficients of μ (B) and $\log \sigma$ (C). × indicates individuals with the absolute value of standarized score greater than 2. (D) Scatte plot of duration. Density plot of parameters and duration are also shown in B, C, and D.

Table 1: Correlation coefficients between μ and $\log\sigma$ ($r_{\mu-\log\sigma}$)

Drug	all data ($n = 51$)	without outliers ($n = 49$)
Pro	−0.308	−0.219
Lid	−0.415	−0.301
Mep	0.012	0.014
Bup	−0.154	−0.160

Table 2: Correlation coefficients of μ (r_μ) and $\log\sigma$ ($r_{\log\sigma}$) among drugs

	all data ($n = 51$)		without outliers ($n = 49$)	
Combination	r_μ	$r_{\log\sigma}$	r_μ	$r_{\log\sigma}$
Pro–Lid	0.590	0.483	0.568	0.416
Pro–Mep	0.358	0.361	0.467	0.336
Pro–Bup	0.392	0.281	0.498	0.257
Lid–Mep	0.599	0.451	0.526	0.414
Lid–Bup	0.566	0.486	0.527	0.466
Mep–Bup	0.501	0.585	0.420	0.559

Table 3: Parameters used in following simulations

Drug	μ_0	s_{μ_0}	$\log\sigma_0$	$s_{\log\sigma_0}$	$r_{\mu-\log\sigma}$	Combination	r_μ	$r_{\log\sigma}$
Pro	68	10	2.2	0.4	-0.22	Pro–Lid	0.57	0.42
Lid	61	7	2.4	0.4	-0.30	Pro–Mep	0.47	0.34
Mep	50	7	2.4	0.4	-0.01	Pro–Bup	0.50	0.26
Bup	30	13	2.5	0.5	-0.16	Lid–Mep	0.53	0.41
						Lid–Bup	0.53	0.47
						Mep–Bup	0.42	0.56

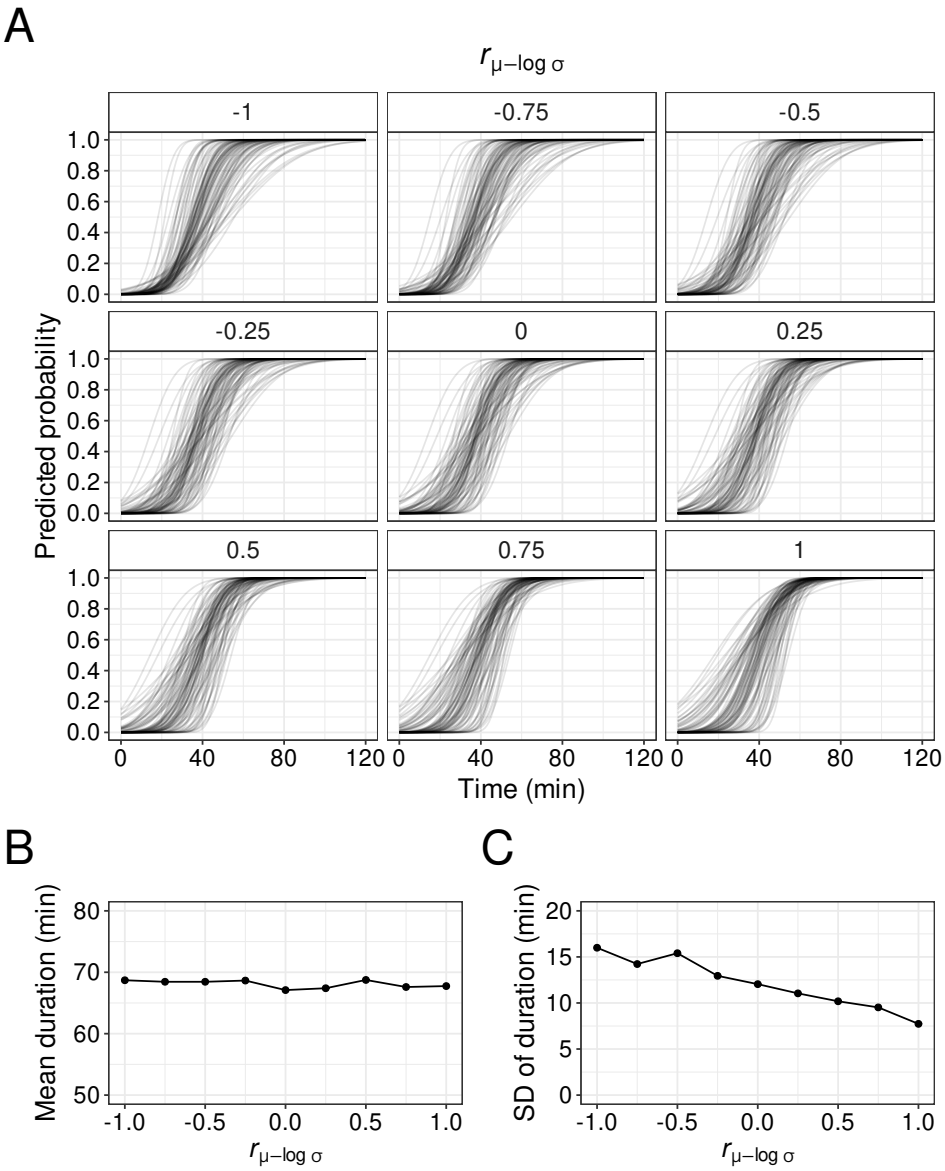

Figure 3: Effect of correlation of parameters between μ and $\log\sigma$ on duration of Lid in simulation. (A) Probability prediction curve by generated parameters (μ and $\log\sigma$) in various $r_{\mu-\log\sigma}$. (B, C) Mean (B) and SD (C) of duration generated by computer simulation in various $r_{\mu-\log\sigma}$.

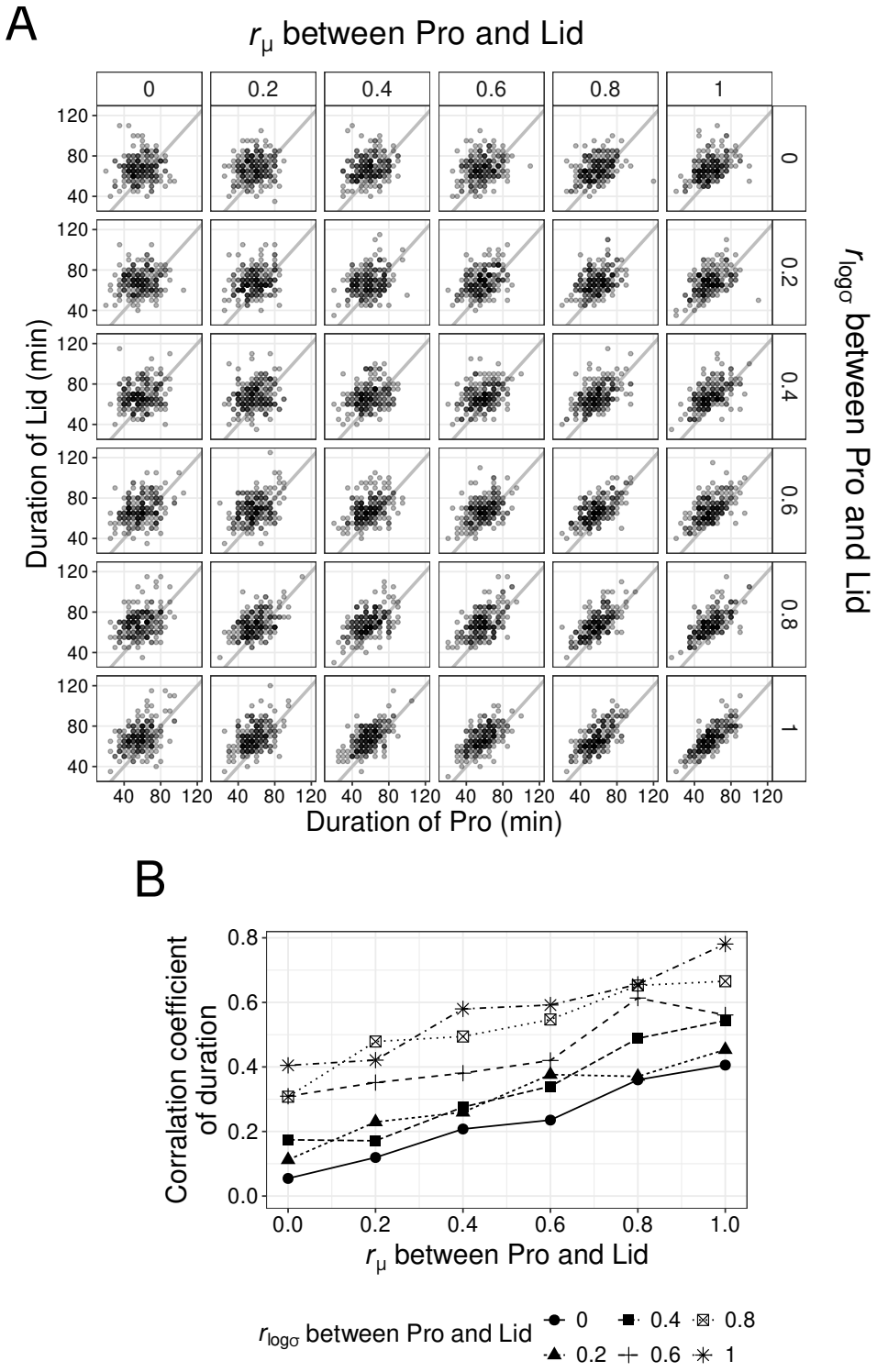

Figure 4: Effect of correlation of parameters (r_μ and $r_{\log\sigma}$) between Pro and Lid on duration in simulation. (A) Relation of durations between Pro and Lid. (B) Correlation coefficients of duration in several parameters. In these experiments, $r_{\mu-\log\sigma}$ was set to 0.

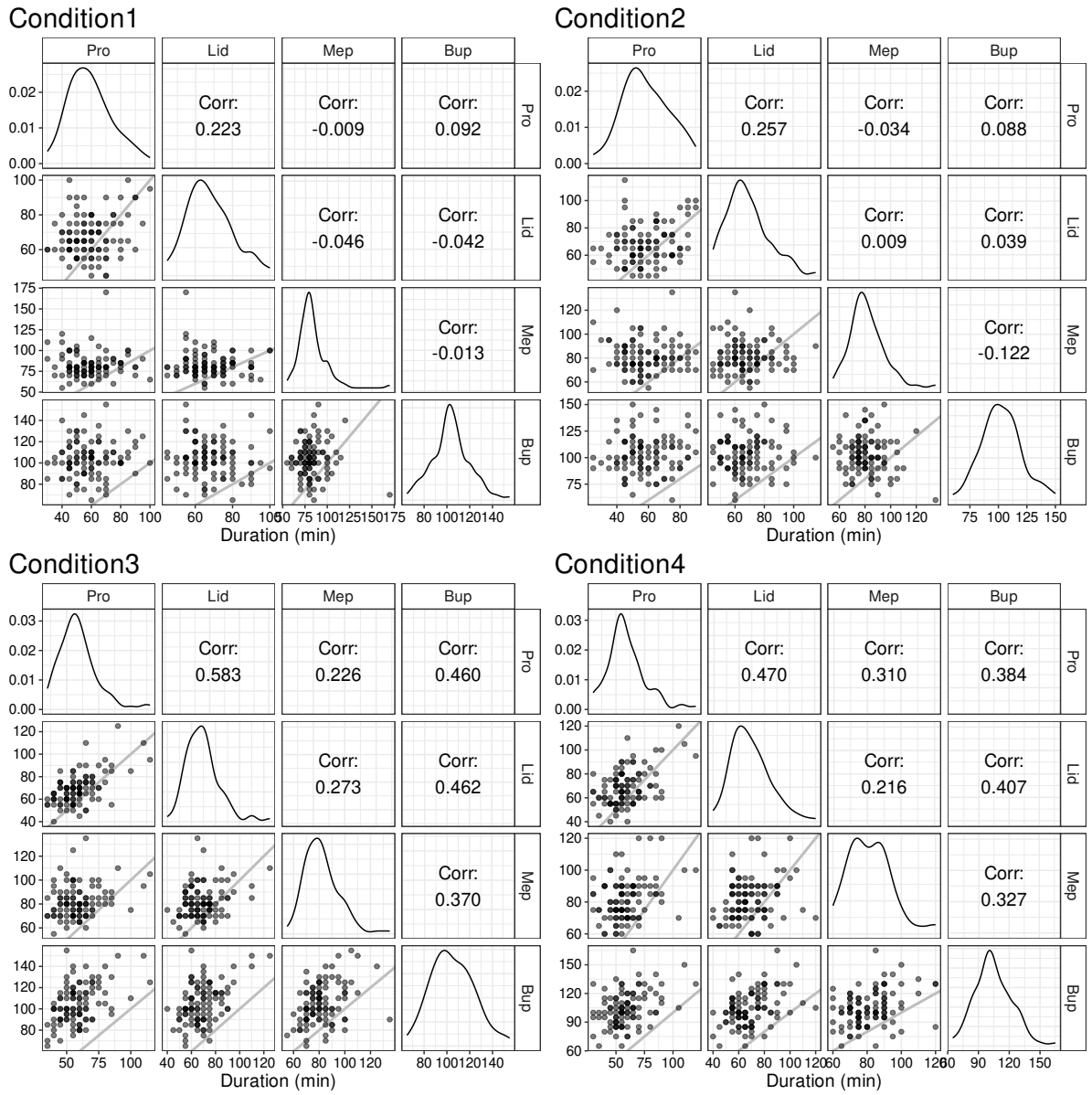

Figure 5: Effect of correlation of parameters among drugs on duration in simulation.

Table 4: Effect of correlation coefficients of parameters on duration among drugs

	Condition 1	Condition 2	Condition 3	Condition 4
$r_{\mu-\log\sigma}$	0	*	0	*
r_{μ} and $r_{\log\sigma}$	0	0	*	*
Pro–Lid	1.223	0.257	0.583	0.470
Pro–Mep	−0.009	−0.034	0.226	0.310
Pro–Bup	0.092	0.088	0.460	0.384
Lid–Mep	−0.046	0.009	0.273	0.216
Lid–Bup	−0.042	0.039	0.462	0.407
Mep–Bup	−0.013	−0.122	0.370	0.327

*Parameters in Table 3 were used.

Table 5: Comparison of duration of local anesthetic agents under each condition

Drug	Condition	n	Events	Median [95% CI]
Pro	Raw data	51	48	55.0 [50.0, 65.0]
	Condition 1	100	100	57.5 [55.0, 60.0]
	Condition 2	100	100	55.0 [55.0, 60.0]
	Condition 3	100	100	55.0 [55.0, 60.0]
	Condition 4	100	100	55.0 [55.0, 60.0]
Lid	Raw data	51	47	60.0 [55.0, 70.0]
	Condition 1	100	100	65.0 [65.0, 70.0]
	Condition 2	100	100	65.0 [65.0, 70.0]
	Condition 3	100	100	70.0 [65.0, 70.0]
	Condition 4	100	100	65.0 [65.0, 70.0]
Mep	Raw data	51	45	85.0 [75.0, 90.0]
	Condition 1	100	100	80.0 [80.0, 80.0]
	Condition 2	100	100	80.0 [75.0, 85.0]
	Condition 3	100	100	80.0 [80.0, 85.0]
	Condition 4	100	100	80.0 [75.0, 85.0]
Bup	Raw data	51	25	– [90.0, –]
	Condition 1	100	100	105.0 [100.0, 105.0]
	Condition 2	100	100	100.0 [100.0, 105.0]
	Condition 3	100	100	100.0 [100.0, 110.0]
	Condition 4	100	100	102.5 [100.0, 105.0]
Lid+Adr	Raw data	51	8	– [–, –]
	Condition 1	100	35	– [–, –]
	Condition 2	100	38	– [–, –]
	Condition 3	100	38	– [–, –]
	Condition 4	100	42	– [180.0, –]

Table 6: Comparison of parameter (μ) and duration between Pro and Lid

	Comparison	Raw data	Condition 1	Condition 2	Condition 3	Condition 4
Parameter	Pro > Lid	31 (60.8%)	69 (69.0%)	73 (73.0%)	79 (79.0%)	80 (80.0%)
	Pro < Lid	20 (39.2%)	31 (31.0%)	27 (27.0%)	21 (21.0%)	20 (20.0%)
Duration	Pro < Lid	29 (56.9%)	68 (68.0%)	67 (67.0%)	75 (75.0%)	70 (70.0%)
	Pro = Lid	6 (11.8%)	5 (5.0%)	4 (4.0%)	9 (9.0%)	11 (11.0%)
	Pro > Lid	15 (29.4%)	27 (27.0%)	29 (29.0%)	16 (16.0%)	19 (19.0%)
	both censored	1 (2.0%)	—	—	—	—

Supplemental Table 1: Spearman's rank correlation coefficients of duration among drugs in animal experiments

Combination	All data ($n = 51$)	Without outliers ($n = 49$)
Pro–Lid	0.592	0.603
Pro–Mep	0.388	0.382
Pro–Bup	0.505	0.509
Lid–Mep	0.508	0.457
Lid–Bup	0.434	0.406
Mep–Bup	0.518	0.498

Supplemental Table 2: Analysis by Linear Mixed-Effects Models with interaction

Effect	Group	Term	Estimate	Std.error	Statistic	df	p.value
fixed		(Intercept)	0.083	0.014	5.841	12.4	0.000
fixed		r_mean	0.398	0.012	31.931	277.0	0.000
fixed		r_logSigma	0.267	0.012	21.445	277.0	0.000
fixed		r_mean:r_logSigma	0.020	0.021	0.973	277.0	0.331
ran_pars	seed_param	sd__(Intercept)	0.034				
ran_pars	Residual	sd__Observation	0.041				

Supplemental Table 3: Spearman's rank correlation coefficients on duration among drugs in each condition

	Condition 1	Condition 2	Condition 3	Condition 4
$r_{\mu-\log\sigma}$	0	*	0	*
r_{μ} and $r_{\log\sigma}$	0	0	*	*
Pro–Lid	0.137	0.200	0.488	0.372
Pro–Mep	0.014	−0.027	0.177	0.262
Pro–Bup	0.083	0.084	0.405	0.356
Lid–Mep	0.013	0.032	0.201	0.201
Lid–Bup	−0.057	0.040	0.367	0.369
Mep–Bup	0.060	−0.061	0.343	0.297

*Parameters in Table 3 were used.

Supplemental Figure 1

Effect of correlation of parameters between μ and $\log \sigma$ on duration of Lid in simulation. (A) Probability prediction curve by generated parameters (μ and $\log \sigma$) in various $r_{\mu-\log \sigma}$. (B) Duration in various $r_{\mu-\log \sigma}$. (C, D) Mean (C) and standard deviation (SD) (D) of duration generated by computer simulation in various $r_{\mu-\log \sigma}$. All results by multiple seed values were indicated.

Supplemental Figure 2

Effect of correlation of parameters (r_{μ} and $r_{\log \sigma}$) between Pro and Lid on duration in simulation. (A) Relation of durations between Pro and Lid. (B) Correlation coefficients of duration in several parameters. In these experiments, $r_{\mu-\log \sigma}$ was set to 0. All results by multiple seed values are indicated.

Supplemental Figure 3

Effect of correlation of parameters among drugs on duration in simulation. All results by multiple seed values are indicated.

Supplemental Figure 4

Survival analysis in all conditions. All results by multiple seed values are indicated.