Estimation of the effect-site equilibration rate constant using the time-to-peak effect of muscle relaxants measured by train-of-four stimulation during general anesthesia induction

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Background: The concept of the effect-site concentration of anesthetic agents is important. The effect compartment model can be explained using the concepts of effect-site concentration and effect-site equilibration rate constant (k_{e0}). This study confirms that the time-to-peak effect (t_{pe}) can be measured easily in clinical practice by applying a priming dose and train-of-four (TOF) during general anesthesia induction, and k_{e0} can be calculated from the t_{pe} of the four muscle relaxants that are commonly used in general anesthesia.

Methods: Eighty patients who received general anesthesia were divided into the succinylcholine, rocuronium, atracurium, or vecuronium groups. Priming doses of muscle relaxants were administered. The effects of muscle relaxants were quantified by recording the twitch response of the adductor pollicis muscle after stimulating the ulnar nerve. The t_{pe} was measured at the lowest TOF value. k_{e0} was calculated from the measured t_{pe}.

Results: The k_{e0} values of the succinylcholine, rocuronium, atracurium, and vecuronium groups were 0.076 (0.030)/min, 0.228 (0.122)/min, 0.062 (0.011)/min, and 0.077 (0.019)/min, respectively.

Conclusions: It is possible to estimate k_{e0} from the t_{pe} of muscle relaxants using a priming dose and TOF during general anesthesia induction.

Keywords: Atracurium; General anesthesia; Rocuronium; Succinylcholine; Train-of-four; Vecuronium.

Introduction

The concepts of time and concentration are important for the administration of drugs used in anesthesia. Safe anesthesia is achieved by accurately understanding the effect time of the drug and the dose-response relationship.

The time at which the effect of the drug begins is known as the onset time of the drug. The time at which the effect is maximized is the time-to-peak effect (t_{pe}). However, since blood is not an effect site of the drug but transports the drug to an effect site, the concept of an effect-site concentration that can represent the effect is needed. When the drug is administered, the plasma concentration gradually decreases from the maximum value, and the effect-site concentration gradually increases. The t_{pe} is the time at which the plasma concentration and the effect-site concentration are equal, and the effect-site concentration is maximum [1].

The effect compartment model was designed to explain the effect-site concentration. The effect-site equilibration rate constant (k_{e0}), which is derived from this model, is the first-order rate constant between the effect site and plasma.

The traditional approaches to calculating the k_{e0} are the parametric or sequential pharmacokinetic-pharmacodynamic method and the non-parametric pharmacodynamic modeling. The disadvantage of these methods is the need for a wide range of drug effects, which start at baseline, achieve a maximum effect, and then return to baseline. The calculation of the k_{e0} of the drug requires the measurement of the plasma concentration and pharmacokinetic parameters after drug administration combined with the evaluation of the effect of the drug. This approach usually results in an ethically questionable situation or is unfeasible in the clinical setting [2].

The estimation of k_{e0} using t_{pe} is an alternative method [2]. k_{e0} can be estimated by measuring t_{pe} after the administration of a single-dose or by evaluation of the effect-site concentration-response curve during continuous infusion [3,4]. We estimated k_{e0} from the t_{pe} of muscle relaxants using a single priming dose and train-of-four (TOF) during general anesthesia induction. A priming dose was used because identification of the lowest effect of the drug was not possible with an induction dose.

Knowledge of the t_{pe} and k_{e0} of anesthetic agents is important for safe anesthesia. The purpose of this study is to confirm that t_{pe} can be measured easily in clinical practice by applying a priming dose and TOF during general anesthesia induction, and k_{e0} can be calculated from the t_{pe} of the four muscle relaxants that are commonly used in general anesthesia.

Materials and Methods

After receiving approval from the Institutional Review Board (File No. 2015-12-004-001), a written informed consent was obtained from each patient. Eighty patients who were undergoing elective surgery under general anesthesia for non-systemic diseases such as otitis media and chronic rhinitis were selected by referring to another study [5]. All patients belonged to the American Society of Anesthesiologists (ASA) class 1 or 2. Patients with an ASA class 3 or higher, neuromuscular diseases, liver or kidney diseases, and those without a body mass index of 18.5–30.0 kg/m^2 were excluded. Eighty patients who agreed to the study protocol were randomly divided into the succinylcholine, rocuronium, atracurium, and vecuronium groups. Twenty patients were assigned to each group.

Standard monitoring devices such as non-invasive blood pressure (NIBP), electrocardiogram, and pulse oximetry were used in all patients, who remained in the supine position in the operating room. A kinemyography (KMG) (NMT Mechanosensor, Datex-Ohmeda, Finland) sensor was placed on the thumb and index finger of the arm without the NIBP monitoring device, and electrodes were attached to the wrist where the ulnar nerve passes. After preoxygenation, anesthesia was induced with thiopental sodium 5 mg/kg, 100% oxygen, and 3–5% sevoflurane. The baseline value was measured by stimulating the ulnar nerve with a maximal stimulation of up to 70 mA, and TOF values were monitored every 10 seconds. The muscle relaxants were diluted with normal saline and were prepared as 10 mg/ml of succinylcholine chloride, 10 mg/ml of rocuronium bromide, 10 mg/ml of atracurium besylate, and 1 mg/ml of vecuronium bromide. After one-fifth of the muscle relaxant dose used in the induction of general anesthesia was intravenously administered with a priming dose, the time at which the TOF value was the lowest (Fig. 1A) and the effect-site concentration was the highest (Fig. 1B) was measured and recorded. We used 0.2 mg/kg of succinylcholine, 0.1 mg/kg of rocuronium, 0.1 mg/kg of atracurium, and 0.01 mg/kg of vecuronium as the priming dose. The estimated effect-site equilibration rate constant (estimated k_{e0}) was obtained by using the measured time-to-peak effect (measured t_{pe}). The method of Cortínez et al. [2] was used and is described in the Appendix.

When the TOF value increased to more than 20% of the lowest value, the remaining dose (four-fifths of the total muscle relaxant dose) was intravenously administered. Endotracheal intubation was performed when the TOF value was 0%. Data were collected in real-time using a data collection program (S/5$^®$ collect, Datex-Ohmeda, Finland).

The estimated k_{e0} was obtained from the measured t_{pe}, and all values were expressed as the mean (SD). Statistical analysis was carried out using Statistical Package for Social Sciences$^®$ Statistics version 24 (IBM$^®$, USA). P values smaller than 0.05 were considered statistically significant.

A second objective of the study was the comparison of the

estimated k_{e0} value (obtained from the measured t_{pe}) with the effect-site equilibration rate constant proposed in other studies (presented k_{e0}) [6–9]. The estimated t_{pe} can be calculated from the presented k_{e0} using some equations (detailed in the Appendix). The measured and estimated t_{pe} and the presented and estimated k_{e0} within each group were compared using a one-sample t-test.

Results

The patient characteristics of the four muscle relaxant groups are shown in Table 1. There were no significant differences in these variables between the groups.

The measured t_{pe} of each group was 2.2 (0.4) min in the succinylcholine group, 5.1 (1.7) min in the rocuronium group, 9.6 (1.5) min in the atracurium group, and 9.6 (2.1) min in the vecuronium group. The estimated k_{e0} was 0.076 (0.030)/min in the succinylcholine group, 0.228 (0.122)/min in the rocuronium group, 0.062 (0.011)/min in the atracurium group, and 0.077 (0.019)/min in the vecuronium group.

Table 2 presents the results of the comparison of the estimated k_{e0} and measured t_{pe} with the effect-site equilibration rate constant proposed in other studies (presented k_{e0}) [6–9] and the time-to-peak effect, which is calculated from the presented k_{e0} (estimated t_{pe}). The t_{pe} of the succinylcholine group and the k_{e0} of the vecuronium group were not significantly different, but these variables were significantly different in the other groups.

Discussion

Knowledge about the t_{pe} and k_{e0} of anesthetic agents is important for safe anesthesia. Identification of the time of onset of a drug is easy clinically, but the determination of t_{pe} is not easy. This study was designed to easily obtain the t_{pe} and k_{e0} of anesthetic agents in clinical practice. In general anesthesia induction involving a priming dose, TOF was used to measure t_{pe}. We developed a program using Excel® 2007 (Microsoft, USA) software with equations (shown in the Appendix) that can calculate k_{e0} from t_{pe}. k_{e0} is estimated when t_{pe} is input to the program. The study design and the program can be simulated to obtain the k_{e0} of other drugs, and herein we estimated the k_{e0} of the four muscle relaxants that are commonly used in anesthesia. The measured t_{pe} of the muscle relaxants was obtained by TOF monitoring during general anesthesia induction and administering a priming dose of each muscle relaxant. According to the principle of linear pharmacokinetics, because plasma concentration or
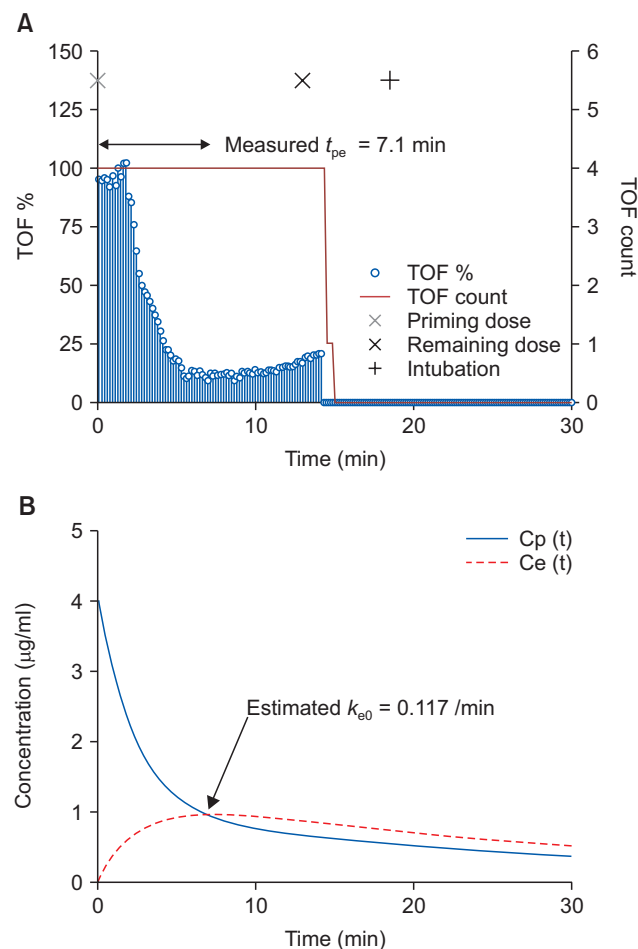

Fig. 1. (A) Graphic representation of the induction-course of a rocuronium-induced non-depolarizing neuromuscular blockade in one patient. Measured t_{pe} is the time-to-peak effect obtained by using train-of-four (TOF). (B) Concentration and time course of plasma Cp(t) and effect-site Ce(t). Estimated k_{e0} is the value calculated using the measured time-to-peak effect.

Table 1. Patient Characteristics

	Succinylcholine group (n = 20)	Rocuronium group (n = 20)	Atracurium group (n = 20)	Vecuronium group (n = 20)
Age (yr)	48 (17)	47 (16)	48 (17)	51 (11)
Sex (M/F)	13/7	13/7	14/6	7/13
Body weight (kg)	64.7 (13.1)	65.5 (14.7)	65.8 (8.3)	64.2 (12.5)
Height (cm)	163.7 (10.6)	162.5 (11.6)	164.9 (7.3)	160.0 (8.3)

Values are expressed as mean (SD).

Table 2. Comparison of the Time-to-peak Effect (t_{pe}) and the Effect-site Equilibration Rate Constant (k_{e0}) for Each Muscle Relaxant

	Succinylcholine group (n = 20)	Rocuronium group (n = 20)	Atracurium group (n = 20)	Vecuronium group (n = 20)
Measured t_{pe} (min) ↓	2.2 (0.4)	5.1 (1.7)	9.6 (1.5)	9.6 (2.1)
Estimated k_{e0} (/min)	0.076 (0.030)	0.228 (0.122)	0.062 (0.011)	0.077 (0.019)
Estimated t_{pe} (min) ↑	2.3	6.3	8.7	8.4
Presented k_{e0} (/min)	0.058	0.127	0.068	0.085
P value*	0.127	0.005	0.013	0.020
P value †	0.013	0.002	0.027	0.066

Values are expressed as mean (SD). Measured t_{pe} is the t_{pe} obtained by using train-of-four (TOF). Estimated k_{e0} is the value calculated using the measured t_{pe}. Estimated t_{pe} is the value calculated using the presented k_{e0}. Presented k_{e0} is the k_{e0} proposed in other studies. References of the presented k_{e0} (/min): succinylcholine [6], rocuronium [7], atracurium [8], vecuronium [9]. →: the direction of calculation, t_{pe} (min): time-to-peak effect, k_{e0} (/min): effect-site equilibration rate constant. *Comparison of the measured t_{pe} and the estimated t_{pe}. †Comparison of the presented k_{e0} and the estimated k_{e0}.

elimination is proportional to the dose, k_{e0} is not affected [10]. Therefore, k_{e0} can be obtained by the intravenous administration of the priming dose.

The TOF stimulation method is used to determine the quantitative relationship between the effect-site concentration and the drug effect. After bolus administration of the muscle relaxant, the time at which the TOF value is the lowest is the t_{pe}. The advantages of TOF stimulation are its noninvasiveness, ease of use, and cost-effectiveness. TOF stimulation has been applied with a minimum interval of 10 seconds and is known to be more sensitive than single twitch [11–13]. In addition, TOF stimulation is more advantageous than single twitch because the latter needs to establish a baseline value before the administration of muscle relaxants. Mechanomyography (MMG) has long been regarded as the gold standard of neuromuscular monitoring, but the mechanomyogram is relatively bulky and difficult to apply, which limits its clinical use [14,15]. The KMG used in this study can be easily applied in clinical practice without significant differences from the results of MMG, electromyography (EMG), acceleromyography, and phonomyography [15–17]. However, some studies suggest that KMG rather than EMG is overestimated [18], which may be a limitation of this study.

The determination of the estimated k_{e0} from the measured t_{pe} only requires a portion of the response curve, without the need to evaluate the complete course of the drug effect, and is possible by measuring the drug effect during general anesthesia induction [19]. Excel® 2007 (Microsoft, USA) software was used to calculate the estimated k_{e0} rather than an expensive commercial program. Excel® is relatively easy to use to obtain the estimated k_{e0} from the measured t_{pe}, and the estimated k_{e0} can be simulated for drugs other than muscle relaxants.

Since the drug volume of distribution in the effect site can be determined from the k_{e0}, the initial loading dose and t_{pe} can be

obtained, and additional dosages and time points can be determined. Therefore, k_{e0} of muscle relaxants is important in general anesthesia. In other words, the t_{pe} and k_{e0} of muscle relaxants are used clinically to determine the timing of intubation of each muscle relaxant and help to determine when additional doses should be administered during anesthetic maintenance. k_{e0} can also be used for target-controlled infusion [1].

Because the estimated k_{e0} was obtained from the measured t_{pe} of the four muscle relaxants commonly used in general anesthesia, it has significance as the estimated k_{e0} of each muscle relaxant in the same study design. Our results indicated a variation in the measured t_{pe} for each patient even with the same muscle relaxant. Since the estimated k_{e0} was obtained from each measured t_{pe}, the former was also affected by an individual bias. However, even in cases in which the same drug was administered at the same dose, the effects were different for each patient because of the pharmacokinetic and pharmacodynamic variability [1]. Pharmacokinetic variability is defined as the condition in which a time-concentration curve varies from person to person. Pharmacodynamic variability is defined as a condition in which a response varies from person to person at the same concentration. This limitation can be overcome by population analysis. However, although studies have suggested the various pharmacokinetic parameters, we selected the same pharmacokinetic parameters for each group of muscle relaxant [6,20–22]. Therefore, it was thought that there was no variation in the estimation of the k_{e0} by using pharmacokinetic parameters.

The second objective of our study was to compare the t_{pe} and k_{e0} of other studies with the t_{pe} and k_{e0} of our study to support the accuracy of our results. The t_{pe} of the succinylcholine group and the k_{e0} of the vecuronium group were not significantly different, but these variables were significantly different in the other groups (Table 2). In the rocuronium group, the presented

k_{e0} that we quoted in another study was 0.127/min, but k_{e0} values suggested in that study were 0.127/min and 0.09/min [7]. For atracurium, a study suggests a k_{e0} of 0.043/min [23], the other study proposes 0.068/min. The difference between this study and other studies is the use of isoflurane or propofol as the anesthetic agent as well as the use of TOF or single twitch. As inhalation anesthetics enhance the effect of muscle relaxation, they likely affect the muscle relaxation effect. TOF stimulation and single twitch were considered study variants with a high sensitivity but a low specificity.

The estimated k_{e0} was compared with the presented k_{e0}, and the estimated t_{pe} (calculated from the presented k_{e0}) was verified by using the measured t_{pe}. In this study, the estimated k_{e0} of succinylcholine, rocuronium, and atracurium was different from the presented k_{e0}. Further studies are necessary to elucidate these results.

In conclusion, this study was designed to easily obtain the t_{pe} and k_{e0} of anesthetic agents in clinical practice. The study design and the program can be simulated to obtain the k_{e0} of other drugs, and we estimated the k_{e0} of the four muscle relaxants that are commonly used in anesthesia. The estimated k_{e0} can be obtained from the measured t_{pe} of these four muscle relaxants using a priming dose and TOF stimulation during general anesthesia induction, and individual deviations in t_{pe} and k_{e0} are observed.

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Appendix

The plasma concentration (C_p) is a composite convolution of the dosage regimen (D) and the unit disposition function (UDF). C_p can be summarized by the following equation:

$$C_p(t) = D(t) \otimes UDF(t)$$ Equation 1

where $\otimes$ represents a convolution. When t is 0 and D is 1, $C_p(t)$ becomes $UDF(t)$. The $UDF(t)$ of the multi-compartment model is presented by the following equation [10]:

$$UDF(t) = \sum_{i=1}^{n} A_i \times e^{-\lambda_i \times t}$$ Equation 2

where A_i is the coefficient and λ_i is the exponent, and these variables are obtained from the volume (V_i) and the micro-rate constant (k_{ij}) shown in Table A.

In the compartment models, the effect-site compartment includes the effect-site equilibration rate constant (k_{e0}), and the volume of the effect site and the drug movement with the central compartment are negligible. The effect-site concentration (C_e) is represented by the following equation [10]:

$$C_e(t) = D(t) \otimes \sum_{i=1}^{n} \frac{k_{e0} \times A_i}{k_{e0} - \lambda_i} \times (e^{-\lambda_i \times t} - e^{-k_{e0} \times t})$$ Equation 3

Since the rate of increase or decrease of the effect-site concentration is 0 at the time-to-peak effect (t_{pe}), when $C'_e(t)$ is 0, t is t_{pe}. The t_{pe} is estimated by substituting k_{e0} into the following equation [10]:

$$C'_e(t) = D(t) \otimes \sum_{i=1}^{n} \frac{k_{e0} \times A_i}{k_{e0} - \lambda_i} \times (\lambda_i \times e^{-\lambda_i \times t} - k_{e0} \times e^{-k_{e0} \times t}) = 0$$ Equation 4

In contrast, k_{e0} can be estimated from the measured t_{pe}. Considering that the plasma concentration and the effect-site concentration are in equilibrium at the measured t_{pe}, k_{e0} can be calculated by the following equation [10]:

$$\{C_p(t_{pe}) - C_e(t_{pe})\}^2 \cong 0$$ Equation 5

These equations were used in Excel® 2007 (Microsoft, USA) to construct a simulation program. The program can calculate t_{pe} using k_{e0}, and can derive k_{e0} by substituting t_{pe}. The pharmacokinetic parameters used for each muscle relaxant are shown in Table A.

Table A. Pharmacokinetic Parameters of Muscle Relaxants

	Succinylcholine: Roy et al. [6]	Rocuronium: Wierda et al. [20]	Atracurium: Kitts et al. [21]	Vecuronium: Sohn et al. [22]
k_{10} (/min)	5.0 (2.6)	0.1	0.166	0.099 (0.049)
k_{12} (/min)	2.9 (3.9)	0.21	0.217	0.23 (0.18)
k_{21} (/min)	1.6 (0.4)	0.13	0.123	0.19 (0.12)
k_{13} (/min)	-	0.028	-	0.086 (0.024)
k_{31} (/min)	-	0.01	-	0.013 (0.007)
V_1 (L/kg)	0.009 (0.003)	0.045	0.032	0.048 (0.02)
V_2 (L/kg)	0.016	0.073	0.068	0.054 (0.031)
V_3 (L/kg)	-	0.126	-	0.38 (0.22)

All data presented as mean (SD). k_{ij} (/min): micro-rate constant. V_i (L/kg): volume of distribution of the three compartments.