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Comparison of Pharmacokinetic Models for Hypnosis Control Based on Effect-Site Propofol Concentration to Maintain Appropriate Hypnosis

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Abstract

This paper studies an appropriate pharmacokinetic (PK) model for hypnosis control based on effect-site anesthetic concentration. For maintaining hypnosis, methods to keep plasma or effect-site concentration of propofol, an anesthetic drug, calculated using PK models at a target level are often used. In order to realize a desirable hypnosis control by such methods an accurate estimation of propofol concentration corresponding to the threshold of unconsciousness is critical. Since time variation of the calculated propofol concentration depends on the PK model, the performance of maintaining hypnosis also depends on it. In this paper, we compare the existing PK models of propofol focusing on sensitivity and specificity for detecting consciousness during anesthesia by a criterion based on calculated propofol concentration and measured aepEX, a hypnosis index. The results show that Barr model provides the highest sensitivity and specificity, and that Marsh, modified Marsh, and Schnider models, which are often used in target controlled infusion systems give fairly high sensitivity and specificity.

Keywords: Anesthesia control; Propofol; Pharmacokinetic model; Target controlled infusion; Effect-site concentration

Introduction

During surgery, patients' hypnosis must be kept at an appropriate level to avoid side effects of anesthetic drugs such as postoperative nausea and vomiting. To realize such hypnosis control, many open-loop and closed-loop control systems have been developed [1-8]. Among them, target controlled infusion (TCI) systems [1], which maintains hypnosis level by keeping anesthetic drug concentration in plasma or effect site at a target level, are often used clinically. During TCI, anesthesiologists determine a target level of anesthetic drug concentration based on their experience and adjust the level according to the patient condition. Therefore, an accurate patient-specific estimation of the appropriate concentration is critical to maintain appropriate hypnosis. Recently, a hypnosis control method that maintains effect-site concentration of an anesthetic drug above a minimum estimate (henceforth minimum effect-site concentration) to keep appropriate hypnosis has been proposed [8]. It also needs an accurate patient-specific estimation of effect-site anesthetic drug concentration to maintain appropriate hypnosis.

There has been a trial [9] to estimate concentration of propofol, a commonly-used anesthetic drug, to maintain appropriate hypnosis using Bispectral Index (BIS) [10]. However, propofol concentration corresponding to appropriate hypnosis cannot easily be obtained from BIS since the very same value does not always indicate the same hypnosis level even though it is being widely used as a hypnosis index and has fairly high reliability. On the other hand, in [8], an estimation method of minimum effect-site propofol concentration using aepEX has been proposed. This estimation method utilizes the property that aepEX barely changes in the range of sufficient hypnosis while it rapidly increases near awakening, hence a good estimate of a patient-specific effect-site propofol concentration for maintaining appropriate hypnosis is expected to be obtained. However, time variation of effect-site propofol concentration depends on pharmacokinetic (PK) models and rate constant (usually denoted by k_{e0}) of propofol elimination from effect-site compartment, and then the accuracy of hypnosis control based on effect-site propofol concentration also depends on them. Therefore, in order to realize a desirable hypnosis control an appropriate PK model for calculating effect-site propofol concentration must be selected among the existing ones. In [8], some existing PK models with the specific rate constant of effect-site compartment were compared from the viewpoint of the accuracy of distinction between unconscious and conscious states based on a small number of clinical data. However, it is not sufficiently clear what is the best PK model because only a limited number of them are considered and because each rate constant is not adjusted for clinical data.

In this paper, we study which is the best model to calculate propofol concentration for effect-site concentration-based hypnosis control. Based on further clinical data, we evaluate the effectiveness of most existing PK models with the best rate constant, which provides the same peak time of propofol concentration as that of measured aepEX, by comparing sensitivity and specificity for detection of consciousness according to a criterion based on effect-site propofol concentration and aepEX.

This paper is organized as follows. First, PK models, relation between effect-site propofol concentration and aepEX, and comparison method of PK models are explained in methods. The comparison results are presented in results, and discussion on these results is given in discussion. Finally, conclusion gives summary of the paper and future work.

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Methods

Pharmacokinetic models of propofol

A pharmacokinetic model of propofol consists of a central compartment, two peripheral compartments, and an effect-site compartment as shown in Figure 1. The differential equation of the model is given by

$$\frac{dx(t)}{dt} = Ax(t) + Bu(t-L)$$

$$x(t) = \left[x_1(t) \quad x_2(t) \quad x_3(t) \quad x_4(t)\right]^T$$

$$A = \begin{bmatrix} -k_1 & k_{21} & k_{31} & k_{41} \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ k_{14} & 0 & 0 & -k_{41} \end{bmatrix}$$

$$B = \left[1/V_1 \quad 0 \quad 0 \quad 0\right]^T$$

where x_i is propofol amount in the compartment i (i =1,2,3,4;1,2,3 and 4 denote the central, shallow peripheral, deep peripheral, and effect-site compartments, respectively), u is infusion rate of propofol, L is a dead time due to movement of propofol in an intravenous fluid line, distribution of propofol in blood vessels and calculation time of aepEX; $k_1 = -k_{10} - k_{12} - k_{13} - k_{14}$ and k_{ij} is rate constant from compartment i to j (0 means elimination). The volume V_4 of effect-site compartment is assumed to be one hundredth of the volume V_1 of central compartment [6]. Although many sets of parameters have been proposed [6,11-27], the best parameter set is still open for discussion. In this study, sixteen model parameter sets given in Table 1 are considered.

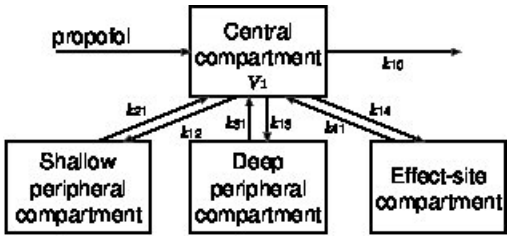

Figure 1: Pharmacokinetic model of propofol. k_{ij} is rate constant from compartment i to j (0 means elimination), and V_1 is the volume of central compartment.

	K_{10}	K_{12}	K_{13}	K_{21}	K_{31}	K_{41}	V_1
Cockshott [13]	0.106	0.144	0.028	0.064	0.0034	0.43	0.25bw
Gepts [14]	0.119	0.114	0.042	0.055	0.0033	1.71	16.9
Kirkpatrick [15]	0.077	0.246	0.039	0.060	0.0019	3.13	0.415bw
Shafer [16]	0.0889	0.062	0	0.0038	0	0.61	0.35bw
Saint-Maurice [17]	0.0508	0.112	0.020	0.045	0.0014	10.3	0.722bw
Tackley [18]	0.0828	0.105	0.022	0.064	0.0034	0.78	0.32bw
Marsh [19]	0.119	0.112	0.042	0.055	0.0033	0.31 (0.26)	0.228bw
Dyck [20]	$\frac{0.652+0.0148\text{bw}}{9.64-0.0512\text{age}}$	$\frac{1.68}{9.64-0.0512\text{age}}$	$\frac{2.67-0.0145\text{age}}{9.64-0.0512\text{age}}$	0.087	$\frac{2.67-0.0145\text{age}}{571-1.66\text{age}}$	0.30	$9.64-0.0512\text{age}$
Kataria [21]	0.0854	0.188	0.0634	0.033	0.0038	2.43	0.41bw
Schnider [22]	$\frac{0.0456\text{bw}-0.0681\text{lbm}+0.0264\text{ht}-2.28}{4.27}$	$\frac{2.562-0.024\text{age}}{4.27}$	0.196	$\frac{2.562-0.024\text{age}}{39.623-0.391\text{age}}$	0.0035	0.23 (0.456)	4.27
Schuttler [23] (age ≤60 yr)	$0.346\text{bw}^{0.04}\text{age}^{0.39}$	$0.0942\text{bw}^{-0.09}\text{age}^{0.39}$	$0.0517\text{bw}^{-0.16}\text{age}^{0.39}$	$0.0488\text{bw}^{0.01}$	$0.00033\text{bw}^{0.55}$	0.16	$1.72\text{bw}^{0.71}\text{age}^{-0.39}$
Schuttler (age>60 yr)	$\frac{0.595\text{bw}^{0.75}-0.045\text{age}+2.7}{1.72\text{bw}^{0.71}\text{age}^{-0.39}}$	$0.0942\text{bw}^{-0.09}\text{age}^{0.39}$	$0.0488\text{bw}^{0.01}$	$0.0488\text{bw}^{0.01}$	$0.00033\text{bw}^{0.55}$	0.16	$1.72\text{bw}^{0.71}\text{age}^{-0.39}$
Barr [24]	$\frac{0.0673\text{lbm}-0.0171\text{bw}}{0.601\text{lbm}}$	0.0265	0.0418	0.0025	$\frac{0.0251\text{lbm}}{107\text{bw}-74.6\text{lbm}}$	4.70	0.601lbm
Li [25]	$0.129\left(\frac{\text{bw}}{60}\right)^{1.879}\left(\frac{\text{age}}{50}\right)^{0.836}$	$0.129\left(\frac{\text{bw}}{60}\right)^{1.879}\left(\frac{\text{age}}{50}\right)^{0.836}$	$0.0298\left(\frac{\text{bw}}{60}\right)^{2.13}\left(\frac{\text{age}}{50}\right)^{1.35}$	$0.0171\left(\frac{\text{bw}}{60}\right)^{0.483}$	$12.1\left(\frac{\text{bw}}{60}\right)^{-0.98}\left(\frac{\text{age}}{50}\right)^{-1.35}$	3.91	$12.1\left(\frac{\text{bw}}{60}\right)^{-0.98}\left(\frac{\text{age}}{50}\right)^{-1.35}$
White [26] (male)	$\frac{26.88-0.029\text{age}}{175.5+0.046\text{age}}$	0.112	0.042	0.055	0.0033	0.20	$\frac{26.88-0.029\text{age}}{175.5+0.046\text{age}}$
White (female)	$\frac{37.87-0.198\text{age}}{191.8-0.669\text{age}}$	0.112	0.042	0.055	0.0033	0.23	$\frac{(191.8-0.669\text{age})\text{bw}}{1000}$
Modified-Marsh [27]	0.119	0.112	0.042	0.055	0.0033	0.31 1.21)	15.9
Sawaguchi* [6]	Same as Schuttler	Same as Schuttler	Same as Schuttler	Same as Schuttler	Same as Schuttler	1.93	Same as Schuttler

k_{ij} is rate constant from compartment i to j and V_1 is the volume of central compartment.K_{41} values are determined such that the peak time of effect-site concentration coincides with that of aepEX, and the original K_{41}'s of Marsh, modified Marsh, and Schnider models are given in parentheses. (age: age in year, bw: body weight in kilogram, ht: height in centimeter, lbm: lean body mass)

*Sawaguchi model parameters are the same as Schuttler model for continuous infusion, but different for bolus. See [6] for details.

Table 1: Parameters of considering pharmacokinetic models.

We determine k_{41} (usually k_{41} denoted by k_{eo} under the assumption that propofol in the effect site does not move back to the central compartment) such that the peak time of effect-site propofol concentration coincides with the peak time of aepEX as possible. The obtained k_{41} values for the PK models are given in Table 1. The original k_{eo} for Marsh, Schnider, and modified Marsh models are also given in parentheses in the same table because they are often used in TCI systems. It should be noted that the obtained k_{41} for Marsh and modified Marsh models are the same because all the PK parameters except k_{41} are the same. Moreover, the dead time L is determined so as to maximize cross-correlation of calculated effect-site propofol concentration and measured aepEX during the first ten minutes after anesthesia induction.

Method for comparison of PK models

In this subsection, we first give pharmacodynamics (PD) of aepEX representing a relation between effect-site propofol concentration and aepEX, and then explain a comparison method of PK models from the viewpoint of sensitivity and specificity for detection of consciousness utilizing effect-site propofol concentration and aepEX.

Figure 2 shows an example of a relation between effect-site propofol concentration and aepEX. The effect-site propofol concentration is calculated from its infusion rate using the PK model, i.e. calculated effect-site propofol concentration depends on the PK model parameters. From the figure it is found that aepEX rapidly decreases near an effect-site concentration $c_{e,min}$ and is almost constant above $c_{e,min}$. Since sufficiently low aepEX corresponds to sufficient hypnosis, patients' hypnosis should be sufficient when the effect-site propofol concentration is above $c_{e,min}$. Therefore, such $c_{e,min}$ can be used to differentiate between consciousness and unconsciousness. In [8], $c_{e,min}$ is called the minimum effect-site propofol concentration and estimated utilizing this property.

In the following, we explain our comparison method of PK model parameter sets. Since intraoperative arousal must be avoided during surgery, it is desirable to accurately detect consciousness by effect-site propofol concentration in effect-site concentration-based hypnosis control. Hence, we evaluate the accuracy of each PK model to detect consciousness in order to choose the most suitable PK parameter set. Such accuracy is determined by the following procedure.

1) Define "conscious period" as the period in which a patient is possibly conscious, i.e. both the period of body movement and the period beyond propofol remaining effect (dead time) after infusion is ceased.

2) For each PK model,

a) Maximum effect-site propofol concentration $c_{e,cons}$ during the conscious period is calculated considering dead time included in the response of aepEX.

b) Sensitivity and specificity of the detection of consciousness by the following criterion are calculated.

Criterion: If the current effect-site propofol concentration c satisfies $c<c_{e,cons}$ or aepEX ≥ 56, the patient is conscious. (We choose the threshold of aepEX as 56 according to [28]).

The hatched region in Figure 3 corresponds to consciousness.

c) Choose the most suitable PK parameter sets comparing the obtained sensitivities and specificities.

Retrospectively, the above procedure is applied to clinical data of 25 patients at Kagawa University Hospital who were mostly kept under proper anesthesia. The demographic data of the patients are given in Table 2.

Results

The sensitivities and specificities of the sixteen PK models obtained by the above procedure are shown in Table 3, and, those of Marsh, Schnider, and modified Marsh models with the original k_{e0} are also shown in the same table. Both the highest sensitivity (0.947) and the highest specificity (0.990) for detecting patients' consciousness are provided by Barr model [24], i.e. the best PK model from the viewpoint of detection accuracy of consciousness may be Barr model. However,

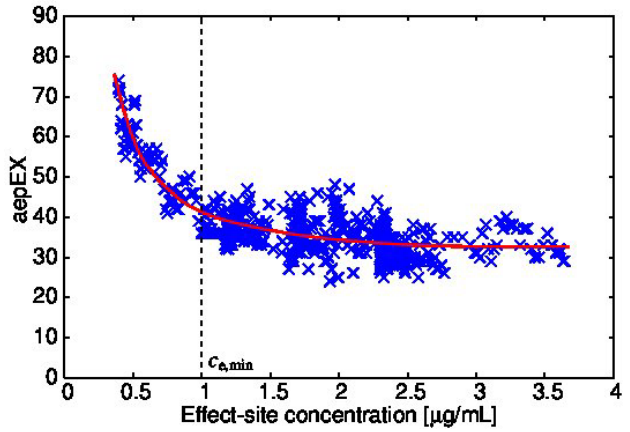

Figure 2: Relation between estimated effect-site propofol concentrations based on the pharmacokinetic model given by Barr et al. [24] and measured aepEX. X indicates measured data and the red curve is an approximated curve of the data.

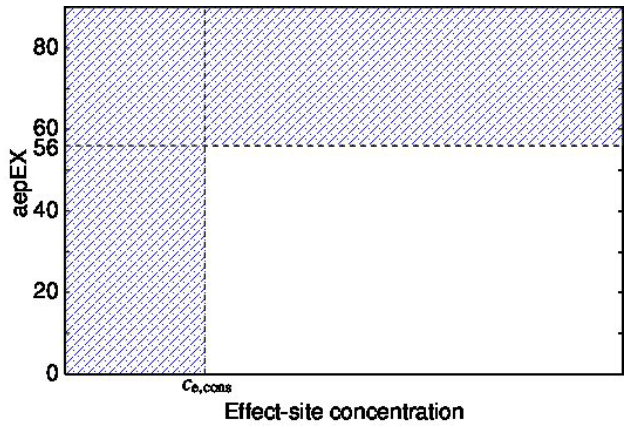

Figure 3: Region corresponding to consciousness on effect-site propofol concentration and aepEX plane.

Male/Female	6/19
age	56.4±13.5 yrs
weight	56.1±10.8 kg
height	156.9±8.2 cm
	(Average ± standard deviation)

Table 2: Demographic data of patients.

Model	Sensitivity	Specificity
Cockshott	0.939	0.955
Gepts	0.929	0.985
Kirkpatrick	0.834	0.935
Shafer	0.908	0.951
Saint-Maurice	0.855	0.932
Tackley	0.941	0.963
Marsh	0.932	0.952
Marsh (original)	0.929	0.946
Dyck	0.837	0.903
Kataria	0.684	0.876
Schnider	0.919	0.968
Schnider (original)	0.909	0.983
Schuttler	0.840	0.879
Barr	0.947	0.990
Li	0.905	0.984
White	0.933	0.958
Modified-Marsh (original)	0.928	0.979
Sawaguchi	0.867	0.969

Table 3: Sensitivities and specificities of PK models for detection of consciousness.

sensitivities for 11 of 16 PK model parameter sets are higher than 0.9, and specificities for 12 of 16 PK model parameter sets are higher than 0.95, and only a few models have unacceptable accuracy.The sensitivities and specificities of Marsh, Schnider, and modified-Marsh models with the original k_{e0} are 0.929 and 0.946, 0.909 and 0.983, and 0.928 and 0.979, respectively, which are fairly high.

Discussion

In the case of concentration-based hypnosis control such as TCI or the method proposed in [8], which keeps effect-site propofol concentration above the minimum effect-site concentration, infusion rate of propofol is determined such that the calculated propofol concentration approaches a target concentration. To realize a desirable hypnosis control accurate estimation of propofol concentration corresponding to the threshold of unconsciousness is critical. Since time variation of propofol concentration is calculated using the PK model, the performance of maintaining appropriate hypnosis depends on it. Therefore, we compare the existing PK models from the viewpoint of detection accuracy of patients' consciousness. We examined sensitivities and specificities for detection of consciousness according to a criterion based on effect-site propofol concentration calculated by the PK models and measured aepEX. Since effect-site propofol concentration is used for maintaining hypnosis, smaller false negative, i.e. higher sensitivity for detection of consciousness is desirable. Barr model provides the highest sensitivity of 0.947, which means that the detection error probability of consciousness is 5.3%, and the best one among the existing PK models. The model also provides the highest specificity of 0.990. This together with the highest sensitivity suggests that it is the best PK model. Moreover, many other models including Marsh, modified Marsh, and Schnider models with the original k_{e0} have fairly high detection accuracy of more than 90%.

For detection of consciousness, we use not only effect-site propofol concentration but also aepEX, because aepEX is an effective hypnosis index to differentiate between consciouness and unconsciousness. Even if the effect-site propofol concentration is sufficiently high, a patient might temporarily be conscious due to strong surgical stimulation. Since consciousness from such a reason must be detected by a hypnosis index, we use aepEX.

Since high specificity means that unconsciousness can be detected with a high probability by using $c_{e,cons}$ as a threshold effect-site concentration for unconsciousness, $c_{e,cons}$ may be appropriate as the target effect-site concentration for TCI systems or the minimum effect-site concentration for the hypnosis control system proposed in [8]. If $c_{e,cons}$ can accurately be estimated during anesthesia, appropriate hypnosis can be achieved by setting the target concentration to $c_{e,cons}$ or more. In [8], an estimation method of the minimum effect-site propofol concentration from clinical data has been proposed; however, it is necessary to establish a more accurate estimation method.

Conclusion

This paper studies the best PK parameter set of the pharmacokinetic model of propofol for hypnosis control based on effect-site anesthetic concentration, and shows that Barr model gives the highest sensitivity and specificity among the existing PK models, i.e. it may be the best model for calculating effect-site propofol concentration. In the future, we will study an estimation method of the threshold effect-site concentration for unconsciousness, and construct a hypnosis control system using it.

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