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Using the Time of Maximum Effect Site Concentration to Combine Pharmacokinetics and Pharmacodynamics

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Background: **To simulate the time course of drug effect, it is sometimes necessary to combine the pharmacodynamic parameters from an integrated pharmacodynamic–pharmacodynamic study (*e.g.*, volumes, clearances, k_{e0} [the effect site equilibration rate constant], C_{50} [the steady state plasma concentration associated with 50% maximum effect], and the Hill coefficient) with pharmacokinetic parameters from a different study (*e.g.*, a study examining a different age group or sampling over longer periods of time). Pharmacokinetic–pharmacodynamic parameters form an interlocked vector that describes the relationship between input (dose) and output (effect). Unintended consequences may result if individual elements of this vector (*e.g.*, k_{e0}) are combined with pharmacokinetic parameters from a different study. The authors propose an alternative methodology to rationally combine the results of separate pharmacokinetic and pharmacodynamic studies, based on t_{peak}, the time of peak effect after bolus injection.**

Methods: **The naive approach to combining separate pharmacokinetic and pharmacodynamic studies is to simply take the k_{e0} from the pharmacodynamic study and apply it naively to the pharmacokinetic study of interest. In the t_{peak} approach, k_{e0} is recalculated using the pharmacokinetics of interest to yield the correct time of peak effect. The authors proposed that the t_{peak} method would yield better predictions of the time course of drug effect than the naive approach. They tested this hypothesis in three simulations: thiopental, remifentanil, and propofol.**

Results: **In each set of simulations, the t_{peak} method better approximated the postulated "true" time course of drug effect than the naive method.**

Conclusions: **T_{peak} is a useful pharmacodynamic parameter and can be used to link separate pharmacokinetic and pharmacodynamic studies. This addresses a common difficulty in clinical pharmacology simulation and control problems, where there is usually a wide choice of pharmacokinetic models but only one or two published pharmacokinetic–pharmacodynamic models. The results will be immediately applicable to target-controlled anesthetic infusion systems, where linkage of separate pharmacokinetic and pharmacodynamic parameters into a single model is inherent in several target-controlled infusion designs.**

INTEGRATED pharmacokinetic–pharmacodynamic studies require carefully gathering blood samples, making frequent measurements of drug effect, and developing complex models of the full pharmacokinetic and pharmacodynamic behavior of the drug.[1] Because integrated pharmacokinetic–pharmacodynamic studies are so difficult and because drug assays typically improve considerably over the useful life of a new drug, the typical research history for an intravenous anesthetic drug involves many pharmacokinetic studies but only one or two integrated pharmacokinetic–pharmacodynamic studies. As a result, the definitive pharmacokinetic study in a population of interest may not incorporate a pharmacodynamic component (*e.g.*, sufentanil pharmacokinetics reported by Gepts *et al.*,[2] propofol pharmacokinetics in children reported by Kataria *et al.*,[3] propofol pharmacokinetics during cardiopulmonary bypass reported by Bailey *et al.*[4]).

Effective use of "pharmacokinetic-only" studies in simulations requires linking them to pharmacodynamic models. The naive way to perform this linking is to simply take the value of k_{e0}, the plasma effect site equilibration rate constant, reported in the integrated pharmacokinetic–pharmacodynamic study, and use this value with the pharmacokinetic parameters of interest to simulating the time course of drug concentration in the effect site. As Gentry *et al.*[5] demonstrated for thiopental, and Wakeling *et al.*[6] demonstrated for propofol, this naive approach is unwise and will lead to very poor predictions of the time course of drug effect.

We propose an alternative approach for combining pharmacodynamic parameters from an integrated pharmacokinetic–pharmacodynamic study with pharmacokinetic parameters from a separate study, based on the time of peak effect, t_{peak}. In this approach, the investigator first translates the k_{e0} reported in the integrated pharmacokinetic–pharmacodynamic study into t_{peak}, the time of maximum effect site concentration following an intravenous bolus dose when there is no drug initially in the system. Of course, if the original study observes and reports t_{peak}, this can be used instead. The investigator then calculates the value of k_{e0} that accurately predicts t_{peak} when used with the pharmacokinetic parameter set of interest. We propose that t_{peak} is a model independent parameter, as it can be directly observed following a submaximal bolus dose. As a model independent parameter, t_{peak} can be used with different pharmacokinetic parameter sets to accurately describe the time course of concentration in the effect site.

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The goal of this article is to evaluate whether the proposed "t_{peak} method" is superior to the naive approach with three often used drugs, remifentanil, thiopental, and propofol, as follows:

1. To compare the predicted effect site concentrations obtained by the two methods, we evaluate two previously published studies of thiopental.[7,8] Each of these studies is an integrated pharmacokinetic–pharmacodynamic study, which allowed examination of the results of exchanging parameters between the studies.
2. We performed a simulation study based on the pharmacokinetics and pharmacodynamics of remifentanil[9] to compare the time course of drug effect and the accuracy of k_{e0} estimates for the two methods.
3. We applied the t_{peak} method to propofol to combine propofol pharmacokinetic parameters[10] that have been demonstrated to be reliable[11] with the k_{e0} from a published pharmacokinetic–pharmacodynamic model.[12,13] These results are directly relevant to the commercially available propofol infusion system Diprifusor (AstraZeneca, London, United Kingdom).

Methods

As a theoretical treatise, this work was not reviewed by an institutional review board. The published studies explored in this analysis were approved by their respective institutional review boards.[7–13]

We suppose that we have available the results from the "best" combined pharmacokinetic–pharmacodynamic study and have selected a "best" pharmacokinetic study that addresses our specific population. The proposed method for combining the results of these two studies is:

1. From the parameters of the "best" combined pharmacokinetic–pharmacodynamic study, calculate t_{peak}, the time of peak effect following submaximal bolus administration. Of course, if t_{peak} has been observed and reported as part of the original study, that value can be used directly.
2. Using the "best" pharmacokinetic parameters calculate an "updated" k_{e0} that preserves the t_{peak} calculated in step 1 or reported in the original study.

The mathematical details of calculating t_{peak} are explored in the Appendix. An intuitive representation follows. Let the concentration of drug in the plasma following a bolus dose of 1 unit have the polyexponential form

$$C_p(t) = \sum_{i=1}^{n} A_i e^{-\lambda_i t}, \qquad (1)$$

with the bolus occurring at time 0, when there is no drug in the system. Note that this model assumes instantaneous mixing. The limitations of this assumption are presented in the Discussion.

Let the concentration of drug in the effect site be related to the concentration in the plasma by a first-order process with rate constant k_{e0}. Note that this assumes a "direct effect" model. Again, the limitations of this assumption are presented in the discussion.

With these assumptions, the concentration in the effect site resulting from a bolus dose of 1 unit is given by

$$C_e(t) = \sum_{i=1}^{n} \frac{k_{e0} A_i}{k_{e0} - \lambda_i} (e^{-\lambda_i t} - e^{-k_{e0} t}). \qquad (2)$$

The time t_{peak} is the time at which C_e reaches its maximum value. Since we are only concerned with the time of maximum effect site concentration, the magnitude of the bolus dose is irrelevant: changing the magnitude changes the maximum concentration, but not the time at which it occurs. Thus, we can think of $C_p(t)$ as the unit disposition function (UDF) of the plasma, and we can think of $C_e(t)$ as the UDF of the effect site. To use t_{peak} in the manner we have described, we are presented with two problems: finding t_{peak} given k_{e0}, and finding k_{e0} given t_{peak}.

In the first problem, finding t_{peak} means finding the time t that maximizes C_e in equation 2, given the pharmacokinetic parameters A and λ. This maximization problem can be solved numerically. For the second problem, finding k_{e0} given t_{peak} and a new vector of pharmacokinetic parameters A and λ, we observe that since t_{peak} maximizes C_e, the derivative of C_e with respect to t must equal zero at $t = t_{peak}$. That is, differentiating equation 2, t_{peak} satisfies

$$\sum_{i=1}^{n} \frac{k_{e0} A_i}{k_{e0} - \lambda_i} (\lambda_i e^{-\lambda_i t_{peak}} - k_{e0} e^{-k_{e0} t_{peak}}) = 0. \qquad (3)$$

Thus, finding k_{e0} means solving equation 3 for k_{e0}, which is done numerically. The Appendix covers a number of important technical mathematical details of finding t_{peak} given k_{e0} and a vector of pharmacokinetic parameters, and finding k_{e0} given t_{peak} and a different vector of pharmacokinetic parameters.

Simulation studies

Thiopental. To compare the naive method with the t_{peak} method of combining pharmacokinetic data from one study with pharmacodynamic data from a second study, we considered the models developed in two previously published studies of thiopental, one by Stanski and Maitre[7] and the other by Shanks *et al.*[8] The two studies are summarized in table 1. In the model of Stanski and Maitre,[7] we chose parameters corresponding to a 35-yr-old, 70-kg subject. The UDF (thiopental concen-

Table 1. Comparative Summary of the Two Thiopental Studies Used to Test Our Methodology

	Stanski and Maitre[7]	Shanks *et al.*[8]
Subject population	Surgical patients and healthy volunteers, including heavy and light drinkers, elderly, and women	Males undergoing minor surgery
Drug input	Intravenous bolus or rapid infusion	Intravenous bolus or rapid infusion
Pharmacokinetic model	Three-compartment mammillary model with input and elimination at the central compartment; some parameters vary with age and weight	Intravenous bolus or rapid infusion. Four-compartment open mammillary model with input to the central compartment and elimination from a peripheral compartment
Pharmacokinetic model estimation technique	NONMEM*	SAAM†
Pharmacodynamic response	95% Spectral edge	Burst suppression of the electroencephalogram and loss of voluntary motor power
Pharmacodynamic model	Sigmoid E_{max}	Sigmoid E_{max}
Pharmacodynamic model estimation technique	Semiparametric estimation of k_{e0}	Parametric estimation of k_{e0}

* NONMEM Software Program, NONMEM Project Group, University of California at San Francisco, California. † SAAM software program, SAAM Institute, Seattle, Washington.

tration, in units of μg/ml, in the plasma following a bolus dose of 1 mg) corresponding to these values is

$$Cp(t) = 0.164e^{-0.688t} + 0.0135e^{-0.0191t} + 0.00335e^{-0.000904t}.$$

In the model by Shanks,[8] the plasma thiopental concentrations over time are described by the following UDF:

$$Cp(t) = 0.28e^{-1.704t} + 0.0127e^{-0.141t} + 0.0158e^{-0.0181t} + 0.00375e^{-0.00165t}.$$

Based on these pharmacokinetic models, we constructed two hypothetical cases and evaluated each using the naive and t_{peak} methodology:

Test Case 1

We imagine that we have the pharmacokinetic and pharmacodynamic results from Shanks *et al.*,[8] and we wish to use their pharmacodynamics (*i.e.*, k_{e0} or t_{peak}) with the "improved" age- and weight-adjusted pharmacokinetic model of Stanski and Maitre.[7] In this test, the full pharmacokinetic–pharmacodynamic model reported by Stanski and Maitre[7] represents the "hypothetical truth," and the test is whether the naive approach or the t_{peak} approach better integrates the pharmacodynamics of Shanks *et al.*[8] with the pharmacokinetics of Stanski and Maitre.[7]

Test Case 2

We imagine that we have the pharmacokinetic and pharmacodynamic results from Stanski and Maitre,[7] and we wish to use their k_{e0} with the "improved" four-compartment pharmacokinetic model of Shanks *et al.*[8] In this test, the full pharmacokinetic–pharmacodynamic model reported by Shanks *et al.*[8] represents the "hypothetical truth," and the test is whether the naive approach or the t_{peak} approach better integrates the pharmacodynamics of Stanski and Maitre[7] with the pharmacokinetics Shanks *et al.*[8]

For both test cases, the goodness of the naive and t_{peak} approaches was assessed graphically.

Remifentanil

We used simulations of remifentanil, for which we have detailed population models,[9] to address the accuracy of the naive and t_{peak} methods of determining the k_{e0} when an improved pharmacokinetic model is developed. We created 100 individuals drawn from the population distribution as described by Minto *et al.*[9] and defined as "true" the time course of plasma and effect site concentration following a 500-μg intravenous bolus of remifentanil. We then simulated a crude pharmacokinetic–pharmacodynamic clinical trial as follows:

1. Simulated blood samples were drawn at 0, 5, 10, 15, 20, 25, 30, 40, and 60 min. No noise was added to the assay.
2. Drug effect was measured concurrent with the blood samples. No noise was added to the "measured" drug effect.
3. A one-compartment pharmacokinetic model was fit to the measured remifentanil concentrations.
4. A k_{e0} link model and a sigmoid E_{max} pharmacodynamic model were fit to the measured drug effect.
5. Two determinations of t_{peak} were made:
   a. Calculated from the model built in step
   b. Directly "observed" during the experiment

We then assumed that an improved pharmacokinetic model was developed in a subsequent pharmacokinetic study. In this case, the improved model was simply the "true" remifentanil pharmacokinetics for each individual, as described above. We examined the time course of

drug effect when the true pharmacokinetic model was combined with three different estimates of k_{e0}:

1. Naive method: k_{e0} determined from the crude study
2. t_{peak} method: t_{peak} calculated from the crude study (4a above)
3. t_{peak} method: t_{peak} directly observed (4b above)

Goodness of each method was assessed graphically and by repeated-measures *t* test of the k_{e0} value *versus* the true value of k_{e0} in each subject.

Propofol

The third test has immediate commercial implications: how to best combine the propofol pharmacokinetic parameters reported by Marsh *et al.*,[10] as presently used in the Diprifusor device, with the pharmacodynamic parameters from the pharmacokinetic–pharmacodynamic model published by Schnider *et al.*[12,13] The pharmacokinetic model reported by Marsh *et al.*[10] has been demonstrated to produce acceptable performance when used to control the administration of propofol[11] and thus is the pharmacokinetic model incorporated into the only commercially approved (outside of the United States) propofol target-controlled infusion pump (Diprifusor). Marsh *et al.*[10] did not concurrently estimate pharmacodynamic parameters, and thus, the question of how to combine the Marsh pharmacokinetic parameters with a propofol pharmacodynamic model is of immediate consequence to the Diprifusor device.

From the pharmacokinetic model reported by Schnider *et al.*,[12] we chose parameters corresponding to a 35-yr-old, 70-kg, 178-cm man. The UDF (propofol concentration, in units of μg/ml, in the plasma following a bolus dose of 1 mg) corresponding to these values is

$$Cp(t) = 0.227e^{-1.03t} + 0.00623e^{-0.039It} + 0.0005e^{-0.00233t}.$$

From the model reported by Marsh *et al.*,[10] we chose parameters corresponding to a 70-kg subject. The UDF corresponding to these values is

$$Cp(t) = 0.0566e^{-0.299t} + 0.0056e^{-0.0301t} + 0.00036e^{-0.00239t}.$$

The question is: What is the best value of k_{e0} to use with the Marsh pharmacokinetics? We assumed, somewhat parochially, that the high-resolution pharmacokinetic–pharmacodynamic study of Schnider correctly characterized the time course of effect site propofol concentration following bolus injection. We compared two different methods of deriving k_{e0} for use with the Marsh pharmacokinetics:

1. Naive method: The k_{e0} reported by Schnider[13] is used with the pharmacokinetics reported by Marsh.[10]
2. t_{peak} method: k_{e0} is calculated for the Marsh pharmacokinetics[10] so that the peak effect site concentration occurs at the same time as the peak effect site concentration reported by Schnider.[13]

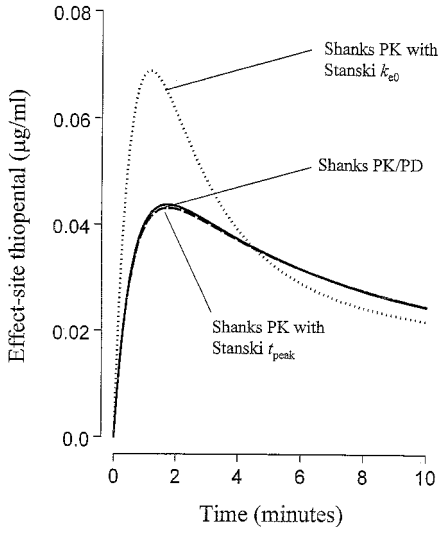

Fig. 1. The effect site unit disposition functions (*i.e.*, response to a 1-mg bolus dose) obtained from the pharmacokinetic (PK)–pharmacodynamic (PD) parameters of Shanks *et al.*[8] (*solid curve*), the pharmacokinetic parameters of Shanks *et al.* and the k_{e0} of Stanski and Maitre[7] (naive method; *dotted curve*), and the pharmacokinetic parameters of Shanks *et al.* and the k_{e0} obtained from the Stanski and Maitre t_{peak} (t_{peak} method; *dashed curve*, nearly indistinguishable from the solid curve).

The goodness of each method was assessed graphically.

All modeling was done with Excel (Microsoft, Redmond, WA), using the "Solver" function and macro routines written by the authors.

Results

Thiopental Simulation Study

Table 1 summarizes the thiopental studies used in the simulations. Figure 1 shows the results of test case 1, in which the "truth" was defined as the pharmacokinetic and pharmacodynamic results from Shanks[8] (solid line). The dotted line shows the results of the naive approach, in which the k_{e0} from the Stanski and Maitre[7] trial (0.58 min^{-1}) has been combined with the pharmacokinetics reported by Shanks *et al.*[8] The naive approach poorly approximates the "true" time course of effect site concentrations. The dashed line shows the result of the t_{peak} approach. The Stanski and Maitre[7] pharmacokinetic–pharmacodynamic model predicts a t_{peak} of 1.75 min. This t_{peak}, when combined with the pharmacokinetic parameters of Shanks *et al.*,[8] yielded a k_{e0} of 0.284 min^{-1}, in close agreement with the value of 0.29 min^{-1} reported by Shanks *et al.*[8] The dashed line is nearly indistinguishable from the solid line that defines the true model, demonstrating that the t_{peak} approach has almost perfectly captured the "true" time course of drug effect.

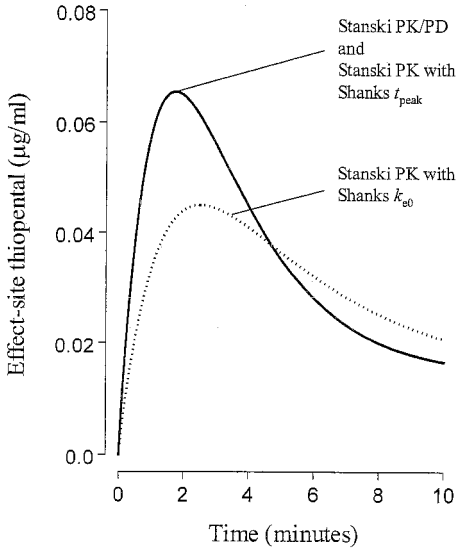

Fig. 2. The effect site unit disposition functions obtained from the pharmacokinetic (PK)–pharmacodynamic (PD) parameters of Stanski and Maitre[7] (*solid curve*), the pharmacokinetic parameters of Stanski and Maitre and the k_{e0} of Shanks *et al.*[8] (naive method; *dotted curve*), and the pharmacokinetic parameters of Stanski and Maitre and the k_{e0} obtained from the t_{peak} of Shanks *et al.* (t_{peak} method; *dashed curve*, indistinguishable from the solid curve).

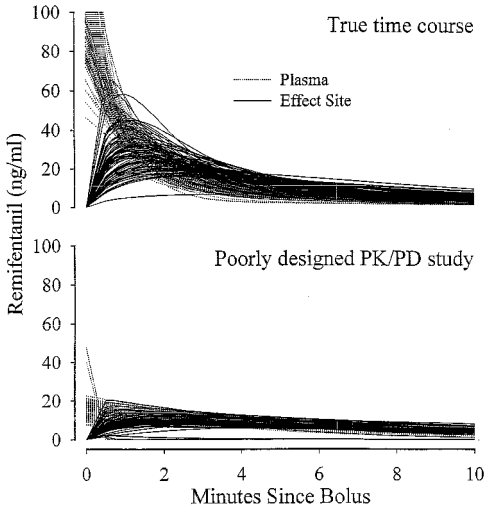

Fig. 3. (*Top*) "True" remifentanil plasma (*dotted lines*) and effect site (*solid lines*) concentrations in 100 individuals, based on the population model reported by Minto *et al.*[9] (*Bottom*) Estimated remifentanil plasma (*dotted lines*) and effect site (*solid lines*) concentrations in the same 100 individuals as shown in the top graph, following a poorly designed pharmacokinetic (PK)–pharmacodynamic (PD) study.

Figure 2 shows the results of test case 2, in which the "truth" was defined at the pharmacokinetic and pharmacodynamic results as reported by Stanski and Maitre[7] (solid line). The dotted line shows the results of the naive approach, in which the k_{e0} reported by Shanks *et al.*[8] (0.29 min^{-1}) has been combined with the pharmacokinetics reported by Stanski and Maitre.[7] The naive approach poorly approximates the "true" time course of effect site concentration. As in figure 1, a dashed line in figure 2 shows the prediction using the t_{peak} approach, in which the time of peak effect reported by Shanks *et al.*[8] has been used to calculate a k_{e0} for use with the pharmacokinetics reported by Stanski and Maitre.[7] The dashed line is not seen in figure 2 because it exactly matches the "true" model, and thus is hidden under the solid line.

In this example, the t_{peak} approach accurately reproduced the "true" time course of drug effect in both simulations. The naive approach did not accurately reproduce the true time course in either simulation.

Remifentanil Simulation

The top graph in figure 3 shows the true values of the plasma concentration (dotted lines) and the effect site concentration (solid lines) for the 100 simulated individuals. The drug effect peaks approximately 1–2 min after bolus injection. The level of interindividual variability is small, reflecting the low variability in remifentanil pharmacokinetics.[9] The average k_{e0} was 0.69 ± 0.039 (SEM) min^{-1}. The lower graph in figure 3 shows the result of the poor pharmacokinetic–pharmacodynamic study in the same 100 individuals. Because the first sample after baseline was taken at 5 min, the initial high remifentanil concentrations were not captured in the pharmacokinetic model, affecting both the apparent time course of remifentanil concentration and the magnitude of the effect site concentrations. The average k_{e0} in the crude study was 2.1 ± 0.15 (SEM) min^{-1}, which was significantly larger than the true values of k_{e0} ($P << 0.001$).

Figure 4 shows the results of the three different approaches to determining the right k_{e0}, given the correct pharmacokinetics in each individual but only the pharmacodynamic results from the crude pharmacokinetic–pharmacodynamic trial shown in the lower graph of figure 3. In the naive approach (top graph), the effect site concentrations uniformly equilibrate too quickly with the plasma, resulting in a predicted effect site concentration that rises to a higher, earlier peak than predicted by the "true" model (fig. 3, top graph). This is the expected result of the consistently larger value of k_{e0} in estimated in the crude pharmacokinetic–pharmacodynamic study. The middle graph in figure 4 shows the predicted effect site concentrations over time using the t_{peak} approach, in which k_{e0} is calculated for each individual to provide the same time of peak effect as predicted by the model parameters of the crude pharmacokinetic–pharmacodynamic study. Despite the crude nature of the study, the time course of concentration in the effect site closely matches the "true" time course shown in the top graph of figure 3. k_{e0} estimated using the calculated t_{peak} was 0.55 ± 0.06 min^{-1}, which was not statistically different from the true values of k_{e0}. The bottom graph in figure 4 shows the predicted effect site concentrations over time using the value of k_{e0} that

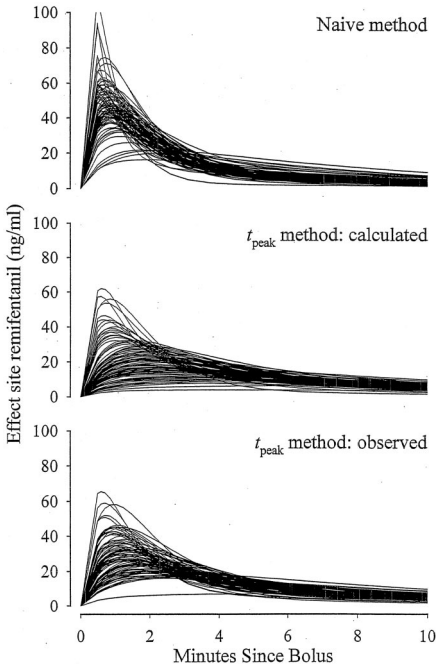

Fig. 4. (*Top*) The results of the naive method, in which the remifentanil effect site concentrations in the same 100 individuals as shown in figure 3 have been calculated using the k_{e0} from a poorly designed trial (fig. 3, *bottom*). (*Middle*) The results of the calculated t_{peak} method, in which the remifentanil effect site concentrations have been calculated using a k_{e0} that predicts the same time of peak effect as predicted by the model from the poorly designed trial. (*Bottom*) The results of the observed t_{peak} method, in which the remifentanil effect site concentrations have been calculated using a k_{e0} that predicts the same time of peak effect as "observed" in the poorly designed trial.

matched the "observed" time of peak effect (*i.e.*, the time of peak effect seen in the top graph of fig. 3). The value of k_{e0} in every individual matched the "true" value of k_{e0} to five significant digits, which was the resolution of the k_{e0} search algorithm. As a result, the time course of drug effect in the lower graph of figure 4 exactly matches the time course shown in the top graph of figure 3.

Propofol Simulation

Figure 5 shows the time course of propofol concentration in the effect site as predicted by the Schnider[12,13] integrated pharmacokinetic–pharmacodynamic model (solid line). The dotted line shows the results of the naive approach, in which the pharmacokinetics reported by Marsh[10] have been combined with the k_{e0} reported by Schnider.[13] The effect site concentrations are too low, and the time of peak effect is almost twice the prediction of the Schnider model.[12,13] The dashed line shows the results of the t_{peak} approach, in which a k_{e0} was calculated for the pharmacokinetics reported by Marsh[10] to give the same time of peak effect as reported by Schnider.[12,13] Although this model does not exactly match the "true" (for these purposes) model reported by Schnider,[12,13] it comes far closer than the naive approach.

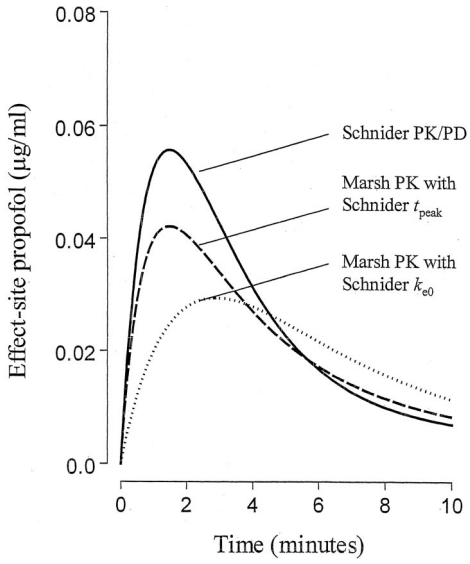

Fig. 5. The effect site unit disposition functions (*i.e.*, response to a 1-mg bolus dose) obtained from the pharmacokinetic (PK)–pharmacodynamic (PD) parameters of Schnider *et al.*[12,13] (*solid line*), the pharmacokinetic parameters of Marsh *et al.*[10] and the k_{e0} of Schnider *et al.* (*dotted line*), and the pharmacokinetic parameters of Marsh *et al.* and the k_{e0} obtained from the t_{peak} of Schnider *et al.* (*dashed line*).

Discussion

Our simulation analyses extends those of Gentry *et al.*,[5] whose work contributed greatly to our thinking. We have shown with three very different simulations that the t_{peak} method of linking disparate pharmacokinetic and pharmacodynamic models is superior to the alternative of simply combining the k_{e0} from one study with the pharmacokinetic parameters from another study. In every simulation, the t_{peak} method yielded k_{e0} estimates closer to the "true" (simulated) k_{e0} values than those obtained by the naive method. As expected, this resulted in a time course of drug effect that also matched the "true" time course of drug effect in each simulation. In the thiopental simulations, the match was so good that the line for the t_{peak} method almost disappeared into the "true" line in the first simulation (fig. 1) and completely disappeared under the "true" line in the second simulation (fig. 2).

None of this should be surprising. It is almost a tautology that linking parameters from two models necessarily will perform worse than an approach that adjusts the parameters to account for differences in the underlying models. This is particularly the case for the time course of drug effect because the estimate of k_{e0} is highly dependent on an accurate description of the pharmacokinetic behavior of the drug. The pharmacokinetic model in turn requires a sound study design and an accurate pharmacokinetic model. If the pharmacokinetic model is "wrong" because of a poor study design or a poor choice of model (*e.g.*, missing the early distribution phase), the estimate of k_{e0} will be affected. In

contrast t_{peak} is potentially directly observable following a submaximal intravenous bolus dose. As shown in the third remifentanil example, a directly observed t_{peak} is a model-independent gold standard for describing with a single parameter the time course of concentration in the effect site.

In the remifentanil example, it may seem tautologic that last approach, using the directly observed time of peak effect, would do the best since the time of peak effect was directly observed and not muddled by the poor determination of remifentanil pharmacokinetics. That is exactly the point: As a directly observed pharmacodynamic variable, the time of peak effect should be accurate and independent of the underlying pharmacokinetic and pharmacodynamic model. The remifentanil simulation was structured to make this point obvious.

The choice of the t_{peak} method is not dependent on the structure of the pharmacokinetic model. Mammillary models have well identified problems in the first few minutes, which are addressed by the use of recirculatory models.[14] The recirculatory model has a very different structure from the simply mammillary model used in our simulations but fundamentally still relates dose to plasma concentration using a unit disposition function. Therefore, time course of concentration in the effect site concentration can still be modeled as the convolution of the plasma concentrations over time against $k_{e0}e^{-k_{e0}t}$, the disposition function of the effect site. The t_{peak} method can be used to find the "correct" value of k_{e0} for use with recirculatory models. One simply finds the value of k_{e0} that predicts the correct time of peak effect following bolus injection.

There are two caveats that need to be mentioned. First, our analysis and the derivation in the Appendix are based on the assumption that the pharmacokinetics are described by an effect site disposition curve with a single peak. It is possible for recirculatory models to have multiple peaks, typically separated by 15–30 s. Given that the typical blood–brain equilibration delay is on the order of at least 30–60 s, the concentrations at the effect site are still likely to be unimodal even with a multimodel plasma drug model. Should injection of a bolus be followed by multiple peaks in the effect site, then it would be necessary to designate the time of peak effect as the time of the first, second, or nth, peak effect. To the best of our knowledge, all anesthetic drugs only produce a single peak drug effect following bolus injection, and so the question of how to handle multiple peaks is not clinically relevant for anesthetic drugs.

Second, we have assumed direct effect models, where the drug effect is an instantaneous reflection of the drug concentration in the effect site. For some effects, such as ventilatory depression, it is much more appropriate to use indirect effect models.[15] Indirect models usually contain imbedded direct effect models, and the time to peak effect for the imbedded direct effect model is easily calculated. Although the direct drug effect is almost never observed with indirect effect models, the calculated t_{peak} could still be used to integrate a new pharmacokinetic study with an existing indirect effect model. With indirect effect models, we still encourage investigators to record the time of the observed peak effect (*e.g.*, time of peak ventilatory depression), which provides a model-independent measure of the time course of drug effect that all derivative pharmacokinetic–pharmacodynamic models should accurately predict.

The question remains as to whether it is preferable to choose a model that is the hybrid of a pharmacokinetic–pharmacodynamic model and the "best" pharmacokinetic model, or simply use the "best" of the available integrated pharmacokinetic–pharmacodynamic models. The issue is that the "improved" pharmacokinetic model often represents a major improvement, as explored in the remifentanil example, which motivates the search for how best to combine the results from different studies. There may be practical reasons as well. For example, AstraZeneca carefully explored which of three pharmacokinetic models produced the smallest performance errors for the Diprifusor.[11] This evaluation was very expensive, and the pharmacokinetic model selected for the Diprifusor has been approved by a variety of regulatory authorities. This regulatory approval means that the model is not likely to change. However, it would be useful for the next generation of Diprifusor to incorporate the concentrations at the site of drug effect. The only option is to combine pharmacokinetics incorporated in the Diprifusor with the best available model of propofol pharmacodynamics.

Struys *et al.*[16] have directly compared the naive and t_{peak} approach to mixing propofol pharmacokinetic and pharmacodynamic models for propofol. They administered propofol to 120 patients, targeting the plasma concentration, the effect site using the naive method for determining k_{e0}, or the effect site using the t_{peak} method for determining k_{e0}. They reported that the "biophase model combining the Marsh kinetics and a time to peak effect of 1.6 min accurately predicted the time course of propofol drug effect." This is a prospective test of the two simulations shown in figure 5, validating in patients the conclusion of our simulation that the t_{peak} approach should work better.

Many individuals have used the programs STANPUMP# and RUGLOOP** for pharmacokinetic and pharmacodynamic simulations. These programs have used the t_{peak} approach for nearly 10 yr.

In summary, we encourage clinical investigators to design studies in which t_{peak} can be directly observed

STANPUMP program. Available at http://anesthesia.stanford.edu/pkpd. Accessed June 14, 2003.

** RUGLOOP program. Available at http://users.belgacombusiness.net/cd033704/index.html. Accessed June 14, 2003.

following bolus injection. This requires administration of submaximal doses so that the peak is not obscured by the drug effect maintaining a plateau at maximum effect. It also requires timing the measure of drug effect so that the peak effect is not missed. For pharmacokinetic and pharmacodynamic studies using continuous infusions rather than boluses, we encourage investigators to calculate and report the time of peak effect predicted in their patients. We also encourage clinical investigators and those simulating drug concentrations to use the t_{peak} method when combining pharmacokinetic and pharmacodynamic parameters from separate studies.

The argument that C_e cannot have two or more local maxima was invented by D. Russell Wada, Ph.D. (Pharsight Corporation, Mountain View, California).

Appendix

In this Appendix, we discuss the details of the theory and implementation required to compute t_{peak} from k_{e0} and *vice versa*. As before, let the concentration of drug in the plasma following a bolus dose with no drug already in the system have the polyexponential form given by equation 1. Time t is always taken to be nonnegative, with the bolus occurring at time 0. The only assumption we make about the parameters in equation 1 is that $A_1, \ldots, A_n$ and $\lambda_1, \ldots, \lambda_n$ are all positive. We can assume without loss of generality that $\lambda_1, \ldots, \lambda_n$ are distinct; if some of the λ_i are equal, we can collect terms in equation 1 to obtain distinct λ_i (with a corresponding reduction in n). Since the λ_i are distinct, we can label $A_1, \ldots, A_n$ and $\lambda_1, \ldots, \lambda_n$ so $\lambda_1 > \ldots > \lambda_n > 0$.

Also as before, we let the concentration of drug in the effect site be related to the concentration in the plasma by a first-order process with rate constant k_{e0}, which we assume to be positive. Then the concentration in the effect site resulting from the bolus is the convolution of $C_p(t)$ and $k_{e0} \exp(-k_{e0} t)$, giving equation 2. We must assume $k_{e0} \neq \lambda_i$ for all i.

Let t_{peak} be the time at which C_e reaches its maximum value. That is, t_{peak} is defined by $C_e(t_{peak}) > C_e(t)$ for all $t \neq t_{peak}$

We begin by proving an important prerequisite to further discussion.

Theorem 1

The time t_{peak} that maximizes $C_e(t)$ exists and is unique.

Proof. The effect site and plasma concentrations are related *via* the differential equation

$$\dot{C}_e(t) = k_{e0}[C_p(t) - C_e(t)],$$

where the dot denotes differentiation with respect to t. Taking the derivative with respect to t on both sides gives

$$\ddot{C}_e(t) = k_{e0}[\dot{C}_p(t) - \dot{C}_e(t)].$$

Referring to equation 1, C_p is a sum of decreasing functions and is therefore decreasing, which means that $\dot{C}_p(t)$ is negative for all t. Let t^* be any critical point of C_e, *i.e.*, a point at which the derivative of C_e equals 0 (assuming, temporarily, that C_e has at least one critical point). Then

$$\ddot{C}_e(t^*) = k_{e0}[\dot{C}_p(t^*) - \dot{C}_e(t^*)] = k_{e0}\dot{C}_p(t^*) < 0$$

so that t^* is a local maximum of C_e. Since all local minima, local maxima, and saddle points of C_e must occur at critical points, we can conclude that C_e has no local minima or saddle points, only local maxima. If C_e has two local maxima, there must be a local minimum between them, which is a contradiction because there are no local minima. Therefore, C_e has at most one local maximum and no local minima or saddle points.

According to the foregoing argument, C_e could still have no local maxima (*i.e.*, C_e could have no critical points), but C_e is nonnegative (since it is the convolution of two nonnegative functions) and equals zero at $t = 0$ and $t = +\infty$. Thus, the only way for C_e to have no local maxima would be for C_e to be zero for all t, which is impossible because of our assumptions that $k_{e0} \leq 0$ and $A_i \geq 0$ for all i.

To summarize, we have shown that C_e increases from its initial value of zero at $t = 0$ to its maximum value at $t = t_{peak}$, then decreases back to zero as $t \to \pm\infty$.

In the use of t_{peak} as discussed in the main body of this article, we are presented with two problems: finding t_{peak} given k_{e0} and finding k_{e0} given t_{peak}. (In both problems we take $A_1, \ldots, A_n, \lambda, \ldots, \lambda_n$ to be given.) We consider the first problem first.

From theorem 1, we know that the function C_e has a unique maximum, which lies somewhere between $t = 0$ and $t = +\infty$. Thus, t_{peak} can be found using any one of several standard algorithms for finding a simple extremum of a function of a single variable[17] (e.g., Ch. 10 of reference 17). All such algorithms require either a starting estimate of t_{peak} or a pair of values between which t_{peak} is known to lie. In the following theorem, we obtain values that are guaranteed to bracket t_{peak}. If only a single starting estimate is needed, any number between the bracketing values can be used.

Theorem 2

The time t_{peak} satisfies the inequalities $(\log k_{e0} - \log \lambda_1)/(k_{e0} - \lambda_1) \leq t_{peak} \leq (\log k_{e0} - \log \lambda_n)/(k_{e0} - \lambda_n)$.

Proof. From equation 2 we can write

$$C_e(t) = \sum_{i=1}^{n} C_{e,i}(t) \tag{4}$$

where

$$C_{e,i}(t) = \frac{k_{e0}A_i}{k_{e0} - \lambda_i}(e^{-\lambda_i t} - e^{-k_{e0}t}),$$

$i = 1, \ldots, n$. The function $C_{e,i}$ is what the effect site concentration would be if $C_p(t)$ were given by just the monoexponential function $A_i e^{-\lambda_i t}$, which is a special case of equation 1. Therefore, theorem 1 applies to $C_{e,i}$, so we know that $C_{e,i}$ increases from 0 at $t = 0$ to its unique maximum at $t = t_{peak,i}$ and then decreases back to 0 at $t = +\infty$.

The time $t_{peak,i}$ at which $C_{e,i}$ reaches its maximum is the time at which the derivative of $C_{e,i}$ goes to 0. The derivative of $C_{e,i}(t)$ with respect to t is

$$\dot{C}_{e,i}(t) = \frac{k_{e0}A_i}{k_{e0} - \lambda_i}(-\lambda e^{-\lambda_i t} + k_{e0}e^{-k_{e0}t}),$$

which equals 0 at $t_{peak,i} = (\log k_{e0} - \log \lambda_i)/(k_{e0} - \lambda_i)$.

Consider the function $f(\lambda) = (\log k_{e0} - \log \lambda)/(k_{e0} - \lambda)$. The derivative of f is

$$f'(\lambda) = \frac{1 - \frac{k_{e0}}{\lambda} + \log\left(\frac{k_{e0}}{\gamma}\right)}{(k_{e0} - \gamma)^2}.$$

Since for any x it holds that $\log x \leq x - 1$ (with equality only at $x = 1$), we have that $f'(\lambda) \leq 0$ [with equality only at $\lambda = k_{e0}$, which we must exclude because $f(k_{e0})$ is undefined], whence f is a decreasing function of λ. Recalling that $\lambda_1 > \ldots > \lambda_n$, it follows that $t_{peak,1} = f(\lambda_1) < \ldots < t_{peak,n} = f(\lambda_n)$.

Next, we consider what happens at $t_{peak,1}$ and $t_{peak,n}$. At $t = t_{peak,1}$, the function $C_{e,1}$ is at its maximum, whereas $C_{e,2}, \ldots, C_{e,n}$ are all still increasing (because $t_{peak,1}$ is the smallest of the $t_{peak,i}$). That is,

$\dot{C}_{e,1}(t_{peak,1}) = 0$, $C_{e,1}(t_{peak,1}) = 0$, whereas $\dot{C}_{e,1}(t_{peak,1}) < 0$, for i = 2, . . . , n. Then by equation 4,

$$\dot{C}_e(t_{peak,1}) = \sum_{i=1}^{n} \dot{C}_{e,i}(t_{peak,1}) > 0,$$

whence C_e is increasing at $t = t_{peak,1}$.

By a similar line of reasoning, at $t = t_{peak,n}$, the function $C_{e,n}$ is at its maximum, whereas $C_{e,1}, \ldots, C_{e,n-1}$ have all begun decreasing (because $t_{peak,n}$ is the largest of the $t_{peak,i}$). That is, $\dot{C}_{e,n}(t_{peak,n}) = 0$, whereas $\dot{C}_{e,i}(t_{peak,i}) < 0$ for i = 1, . . . , n − 1. Therefore, $\dot{C}_e(t_{peak,n}) < 0$, whence C_e is decreasing at $t = t_{peak,n}$.

We have shown that C_e is increasing at $t = t_{peak,1}$ and decreasing at $t = t_{peak,n}$, which means $t_{peak,1} < t_{peak} < t_{peak,n}$ (except that $t_{peak} = t_{peak,1}$ if n = 1), completing the proof.

Theorem 2 concludes our discussion of finding t_{peak} given k_{e0}, which brings us to the inverse problem of finding k_{e0} given t_{peak}. From theorem 1, t_{peak} is defined by $\dot{C}_e(t_{peak}) = 0$. That is, differentiating equation 2, t_{peak} is defined by equation 3. Factoring out k_{e0}, the solutions to equation 3 are $k_{e0} = 0$ (which we do not allow) and the solutions (if there are any) to

$$\sum_{i=1}^{n} \frac{A_i}{k_{e0} - \lambda_i} (-\lambda_i e^{-\lambda_i t_{peak}} + k_{e0} e^{-k_{e0} t_{peak}}) = 0. \quad (5)$$

The following theorem shows that equation 5 has a unique solution for k_{e0} that yields a maximum effect site concentration at time equal to t_{peak}.

Theorem 3

Given t_{peak} (and given $A_1, \ldots, A_n, \lambda_1, \ldots, \lambda_n$), there exists a unique value of k_{e0} such that the maximum of $C_e(t)$ occurs at $t = t_{peak}$.

Proof. By the above discussion, it suffices to show that equation 5 has a unique solution. Denote the left-hand side of equation 5 by $f(k_{e0})$. Then

$$f(0) = \sum_{i=1}^{n} A_i e^{-\lambda_i t}$$

which is positive. In addition, $k_{e0} e^{-k_{e0} t_{peak}}$ tends to zero as $k_{e0} \to +\infty$, so for all sufficiently large k_{e0},

$$-\lambda_i e^{-\lambda_i t_{peak}} + k_{e0} e^{-k_{e0} t_{peak}} < 0.$$

Therefore, $f(k_{e0}) < 0$ for all sufficiently large k_{e0}. Thus, there is at least one solution to the equation $f(k_{e0}) = 0$.

Whereas theorem 1 states that given k_{e0} there exists a unique t_{peak}, theorem 3 states the converse. Together, theorems 1 and 3 prove that there is a one-to-one relationship between t_{peak} and k_{e0}. Moreover, by the proof of theorem 3, t_{peak} is a decreasing function of k_{e0}, so that the inverse function, *i.e.*, k_{e0} as a function of t_{peak}, is also decreasing. These properties agree with our intuition that as the rate constant k_{e0} increases, the time of maximum effect site concentration decreases.

Solving for k_{e0} given t_{peak} means solving equation 5 for k_{e0}. Thus, k_{e0} can be found using any one of several standard algorithms for finding a zero of a function of a single variable [*e.g.*, Ch. 9 of reference 17]. All such algorithms require either a starting estimate of k_{e0} or a pair of values between which k_{e0} is known to lie. We have assumed k_{e0} to be positive, so it remains to find an upper bound for k_{e0}. Such a bound is given in the following theorem. If only a single starting estimate is needed, any number between zero and the bound given by the theorem can be used.

The proof of the theorem makes use of the following inequality for the function log x.

Theorem 4

If $1/2 \le \alpha \le 1$, $\log x \le (x - 1)\alpha$ for all $x \ge 1$.

Proof. It is convenient to treat the case $\alpha = 1$ separately. If $\alpha = 1$, the inequality claimed in the theorem reduces to $\log x \le x - 1$, a standard result.

To begin the proof of the theorem for the remaining cases, let α satisfy $1/2 \le \alpha \le 1$ and define $f(x) = \log x - (x - 1)\alpha$. We need to show $f(x) \le 0$ for all $x \ge 1$. We henceforth take $x \ge 1$. From elementary calculus,

$$\log x = \int_1^x dt/t$$

and

$$(x - 1)^\alpha = \int_1^x \alpha(t - 1)^{\alpha - 1}\, dt.$$

.

Subtracting these integrals,

$$\log x = \int_1^x [1/t - a(t - 1)^{\alpha - 1}]dt = \int_1^x \frac{1 - at(t - 1)^{\alpha - 1}}{t}\, dt$$

writing the integrand over a common denominator. To show $f(x) \le 0$, it suffices to show that the integrand in equation 6 is nonpositive for all $t \ge 1$. Let $g(t) = 1 - \alpha t(t - 1)\alpha^{-1}$, the numerator of the integrand. Because the denominator of the integrand is positive for $t \ge 1$, it suffices to show that the numerator g(t) is nonpositive for all $t \ge 1$.

To show $g(t) \le 0$ for all $t \ge 1$, we show that the maximum value of g(t) for $t \ge 1$ is nonpositive. The derivative of g is

$$g'(t) = -\alpha(at - 1)(t - 1)^{\alpha - 2},$$

which goes to 0 only at $t = 1/\alpha$. The second derivative of g is

$$g''(t) = -\alpha(a - 1)(at - 2)(t - 1)^{\alpha - 3}$$

and $g''(1/a) = -(1 - a)^{\alpha - 2}/a^{a - 4} \le 0$ (recalling $1/2 \le \alpha < 1$). Therefore, the point $t = 1/\alpha$ is a local maximum for g. The value of g at $t = 1/\alpha$ is $g(1/\alpha) = 1 - (1/\alpha - 1)^{\alpha - 1}$. Since $\lim_{t \to 1} g(t) = -\infty$ and $\lim_{t \to +\infty} g(t) = -\infty$, the point $t = 1/\alpha$ is the global maximum for g for $t \ge 1$.

We have shown that $g(1/a) = 1 - (1/a - 1)^{\alpha - 1}$ is the maximum value of g(t) for $t \ge 1$. The inequality $1 - (1/\alpha - 1)^{\alpha - 1} \le 0$ holds if and only if $1/\alpha - 1 \le 1$, which is equivalent to $\alpha \ge 1/2$. Thus, for $1/2 \le \alpha < 1$, the function g(t) is nonpositive for $t \ge 1$, completing the proof.

Using the theorem, we can establish an upper bound for k_{e0}.

Theorem 5

The effect site rate constant k_{e0} satisfies $k_{e0} \le \max(1/t_{peak}, \lambda_n + 1/(\lambda_n t_{peak}^2))$.

Proof. From theorem 2, $t_{peak} \le (\log k_{e0} - \log \lambda_n)/(k_{e0} - \lambda_n)$. We consider two cases, $k_{e0} \le \lambda_n$ and $k_{e0} > \lambda_n$.

First suppose $k_{e0} \le \lambda_n$. We can write

$$\frac{\log k_{e0} - \log \lambda_n}{k_{e0} - \lambda_n} = \frac{\log(\lambda_n/k_{e0})}{\lambda_n - k_{e0}} \le \frac{\lambda_n/k_{e0} - 1}{\lambda_n - k_{e0}} = 1/k_{e0},$$

where the inequality follows from the fact that $\log x \le x - 1$ for any x. Therefore, $t_{peak} \le 1/k_{e0}$, and reciprocating both sides, $k_{e0} \le 1/t_{peak}$.

If instead, $k_{e0} > \lambda_n$, then we can write

$$\frac{\log k_{e0} - \log \lambda_n}{k_{e0} - \lambda_n} = \frac{\log(k_{e0}/\lambda_n)}{k_{e0} - \lambda_n} \le \frac{(k_{e0}/\lambda_n - 1)^{1/2}}{k_{e0} - \lambda_n}$$

applying the theorem with $\alpha = 1/2$. Thus, we have

$$t_{peak} \le \frac{(k_{e0}/\lambda_n - 1)^{1/2}}{k_{e0} - \lambda_n}$$

and solving this inequality for k_{e0} yields $k_{e0} < \lambda_n + 1/(\lambda_n t_{peak}^2)$.

We have shown that either $k_{e0} \leq 1/t_{peak}$ or $k_{e0} \leq \lambda_n + 1/(\lambda_n t_{peak}^2)$, so k_{e0} cannot exceed the greater of these two upper bounds.

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