PK/PD Simulation of the Analgesic Effects of Anti-EGFR Antibodies Panitumumab and Cetuximab using the Effect Compartment Model

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Abstract: The analgesic effects of epidermal growth factor receptor (EGFR) inhibitors have been reported in several studies, and the underlying mechanisms of pain relief, particularly for neuropathic pain, have been gradually clarified. To explain the time profile of the analgesic effects of anti-EGFR antibodies, this study used the effect compartment model, which is currently applied to analgesics and sedatives, to explain the duration of pharmacologic effects. The findings indicate the compartmental pharmacological model can reliably predict the duration of the analgesic effects of anti-EGFR antibodies.

Keywords: Panitumumab, Cetuximab, Epidermal Growth Factor Receptor Inhibitor, Pharmaco kinetics/ Pharmacodynamics, Analgesic Effect, Effect Compartment Model.

INTRODUCTION

Members of the human epidermal growth factor receptor (EGFR) family are therapeutic target of inhibitors (EGFR-Is) used in the treatment of various cancer [1-3]. In addition to their antitumor effects, EGFR-Is have also been reported to produce analgesic effect [4-7], and the mechanism underlying this pain relief, particularly in neuropathic pain, has been gradually elucidated [1, 8-9]. A recent report also described alleviation of nociceptive pain following administration of an anti-EGFR antibody, despite ongoing tumor progression, in patients with advanced colonic cancer [10]. However, to the best of our knowledge, the duration of the analgesic effects produced by anti-EGFR antibodies has not yet been quantitatively predicted. As for the pharmacokinetic/ pharmacodynamics (PK/ PD), injections of opioids [11-15], propofol [16], benzodiazepine sedatives [17], neuromuscular blockers [18-19], and acetaminophen [20] were administered intravenously. The effect-site compartment model has been used to estimate changes in blood concentration and hypothetical effect-site concentrations (C_e) during surgery, based on the compartment model proposed by Sheiner *et al*. [18]. This compartmental model is assumed to reflect drug efficacy under clinical conditions. However, a time lag between drug concentration in the blood and the resulting pharmacological effect has been reported; the effect-concentration relationship progresses in a counterclockwise direction relative to changes in blood concentration, phenomenon termed 'hysteresis' [17]. Although the underlying cause of hysteresis remains unclear, the effect-site compartment is assumed to represent the anatomical and physiological site of drug action, and a rate constant is used to link the blood concentration to the concentration at this effect site. The compartmental drug efficacy model can therefore serve as a surrogate measure for the effect-site drug concentration, which cannot be measured directly in clinical practice [12-20].

Therefore, the present study investigated whether the compartmental drug efficacy model is feasible for evaluating the analgesic effects of two anti-EGFR antibodies, [panitumumab (Pmab) and cetuximab (Cmab)], using previously published data. Two categories of source data were used: (i) blood

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concentration data following intravenous administration of Pmab [21] and Cmab, (ii) time course data on nociceptive or neuropathic pain intensity, assessed using the numeric rating scale (NRS)[1)] following intravenous administration of these agents. To date, the longitudinal time course and the precise pharmacological duration of the analgesic effects produced by anti-EGFR antibodies have not yet been quantitatively simulated or characterized using mechanistic mathematical frameworks, representing a major research gap. Therefore, the primary objective of the present study was to investigate the feasibility of a compartmental drug efficacy model to evaluate and compare the analgesic profiles of panitumumab (Pmab) and cetuximab (Cmab) using previously published clinical data. We hypothesized that an effect-compartment model could mathematically resolve the time-lag (hysteresis) between systemic blood concentration and clinical pain relief, thereby enabling the objective quantification and prediction of their respective equilibration rates and analgesic durations. To test this hypothesis, the study utilized extracted blood concentration data and numerical rating scale (NRS) pain intensity time-course data following the intravenous administration of these two agents.

METHODS

Data on blood concentrations and NRS scores were extracted from previously published graphs [2, 10, 22, 23]. To ensure accuracy and minimize estimation errors, a rigorous process involving detailed manual digitization and cross-verification was implemented. To further ensure accuracy and minimize bias, two researchers independently verified the data using magnified images, and the average values were used. Subsequently, pharmacokinetic parameters and C_e were estimated using a compartmental model (Figure **1**), as detailed in the cited literature.

Specifically, the mass transport of the anti-EGFR antibodies between the compartments after intravenous administration was defined by the following simultaneous differential equations:

$$dX_1/dt=R_0-k_{10}*X_1-k_{12}*X_1+k_{21}*X_2$$

$$dX_2/dt=k_{12}*X_1-k_{21}*X_2$$

$$dX_e/dt=k_{e0}*X_1-k_{e0}*X_e$$

where X_1, X_2, and X_e represent the drug amounts in the central, peripheral, and effect-site compartments, respectively; R_0 is the intravenous infusion rate; and k_{12}, k_{21}, k_{10}, and k_{e0} are the respective first-order transfer and elimination rate constants. The hypothetical effect-site concentration (C_e) was derived by dividing X_e by the volume of the central compartment (V_1).

The Pain Relief Score (PRS) was defined on a 0 to 100 scale, with 0 representing the NRS value immediately before administration and 100 representing the minimum (best) NRS score recorded. Assuming a counterclockwise hysteresis loop can be mathematically resolved by linking C_e to clinical pain relief, the relationship between PRS and C_e was

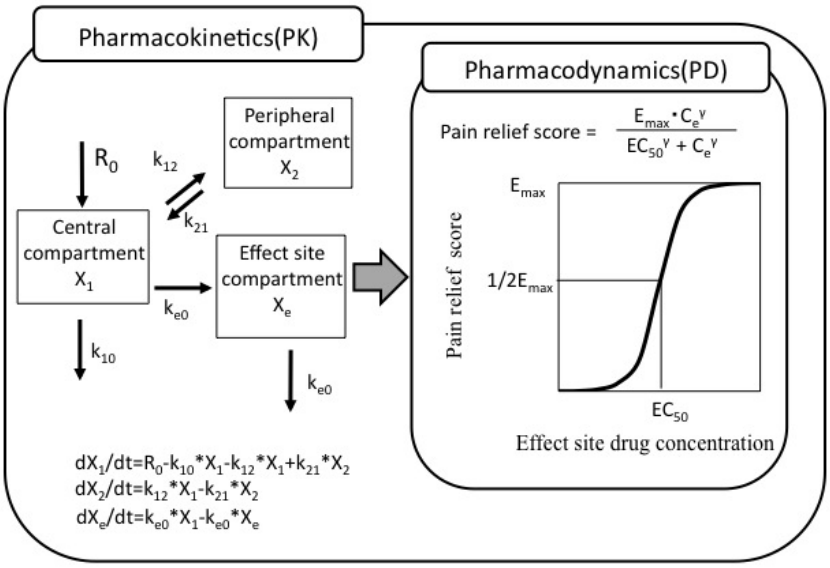

Figure 1: Pharmacokinetic/ pharmacodynamics (PK/ PD) model for intravenous administration of anti-EGFR antibody. k_{12}, k_{21}, k_{10}: rate constants for drug transfer between each compartment (1/day), k_{e0}: equilibrium rate constant governing drug efficacy (1/day), R_0: administration (infusion) rate (mg/day).

Table1: Summary of Source Datasets used for PK/PD Modeling

Drug	Data Type	Sample Size(n)	Cancer Type/Disease	Dosing Regimen	Source Regimen
Pmab	PK	6	Colon or rectal cancer	6mg/kg Q2W	Doi *et al*. 2009 [22]
	PD	1	Colon cancer	6mg/kg Q4W	Yuasa *et al*. 2016 [10]
Cmab	PK	13	Colorectal cancer	400mg/m^2 Q2W	Tabemero *et al* 2010 [23]
	PD	14	Non cancer / CNs[1] or CRPS[2]	400mg/m^2 Q4W	Kersten *et al*. 2019 [3]

[1]CNs: Neuropathic pain due to compressed nerves, [2]CRPS: Complex regional pain syndrome.

simulated using a standard sigmoid E_{max} model equation (Figure **1**):

$$PRS= (E_{max} \cdot C_e^{\gamma})/(EC_{50}^{\gamma} + C_e^{\gamma})$$

where E_{max} is the maximum achievable pain relief score, EC_{50} is the effect-site concentration producing 50% of E_{max}, and γ is the Hill coefficient dictating the sigmoidicity of the curve. The equilibration rate constant k_{e0} and the pharmacodynamic parameters E_{max}, EC_{50}, and γ were estimated using the nonlinear least-squares Solver function in Microsoft Excel, by minimizing the difference between the PRS values predicted by the sigmoid curve equation and the actual measured clinical values [15].

The time course of C_e was then reconstructed from the estimated k_{e0} values as follows. For Cmab, because NRS values were available for both the treatment and placebo groups, the between group difference in NRS values was used to isolate the drug-specific effect. For Pmab, no placebo-controlled data was available in the literature; the absolute NRS value recorded after Pmab administration was used directly. The time to maximum (t_{emax}) and half-life effect-site equilibration ($t_{1/2}k_{e0}$) of C_e were calculated for both agents following 1h intravenous infusion. The duration of the analgesic effect was defined as five times the estimated effect-site equilibration half-life (5 times $t_{1/2ke0}$). This definition is rigorously grounded in standard clinical pharmacological consensus, which dictates that a period of five half-lives allows for more than 96.9% of the drug to be eliminated from the effect compartment [24]. Consequently, this timeframe marks the return of effect-site concentrations to near-baseline levels, serving as a reliable surrogate for the clinical termination of specific pharmacological activity.

To evaluate the mathematical reliability and precision of the model fitting, the coefficient of determination (R^2) and root mean square error (RMSE) were calculated for both the pharmacokinetic (PK) and pharmacodynamic (PD) simulations (Table **2**). Furthermore, clinical background information, including sample sizes, cancer types, and dosing regimens, was extracted from the source literature to ensure the contextual transparency of the analyzed datasets (Table **1**).

Table 2: Pharmacokinetic and Pharmacodynamic Parameters of Anti-EGFR Antibodies

Parameter	Pmab	Cmab
α(1/day)	0.852	1.03
β(1/day)	0.118	0.125
V_1(L)	3.03	-
V_1(L/m^2)	-	1.73
k_{21}(1/day)	0.698	0.775
k_{e0}(1/day)	0.185	0.307
t_{emax}(day)	4.45	6.38
$t_{1/2}k_{e0}$(day)	3.75	2.26
$t_{1/2}k_{e0}$ x 5(day)	18.8	11.3
Pharmacokinetics (PK) Model		
R^2	0.999	0.986
RMSE	0.922	8.247
Pharmacodynamics (PD) Model (PRS)		
E_{max}	82.6	92.8
EC_{50}(ng/mL)	1.62	0.94
γ	34.3	5.62
R^2	0.750	0.487
RMSE	0.104	0.026

EGFR: Epidermal growth factor receptor; Pmab: Panitumumab; Cmab: Cetuximab.
[a]Calculated from the blood concentration graph of Pmab in the previous report [22]. This calculation was made using the NRS values previously reported [10].
[b]Calculated from the blood concentration graph of Cmab in the previous report [23]. This calculation was made using the NRS values previously reported [3].

RESULTS

The calculated PK and PD parameters of Pmab and Cmab, along with the model goodness-of-fit statistics (R^2 and RMSE) and the clinical characteristics of the original datasets, are summarized in Table **2**. Both PK models demonstrated excellent reproducibility with high R^2 and low RMSE values (R^2 = 0.999, RMSE = 0.922

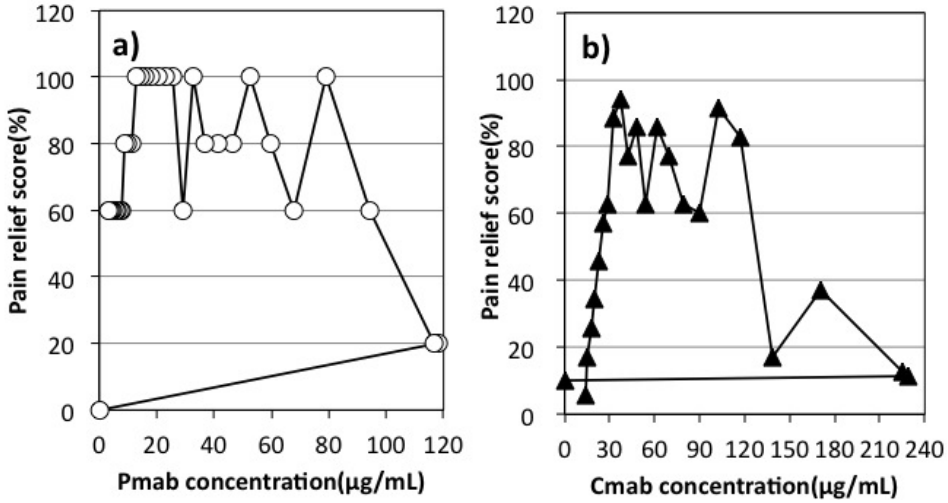

Figure 2: Relationship between anti-EGFR antibody blood concentration and pain relief score.

a) After intravenous administration of Pmab.

b) After intravenous administration of Cmab.

for Pmab; R^2 = 0.986, RMSE = 8.247 for Cmab). The PD model fitting for PRS also reliably captured the chronological drug efficacy profiles, yielding an R^2 of 0.750 (RMSE = 0.104) for Pmab and an R^2 of 0.487 (RMSE = 0.026) for Cmab (Table **2**). Using these parameters, the relationship between blood concentration and PRS following 1h intravenous infusion of Pmab and Cmab is shown in Figure **2**. A counterclockwise progression effect relative to blood concentration change [17] was confirmed in both cases. When NRS values after Cmab administration alone were calculated, the resulting value (0.313 [1/day]) was nearly identical to that obtained using the placebo-corrected data. The time profiles of blood concentration, C_e, and PRS are shown in Figures **3** and **4** for Pmab and Cmab, respectively. The combined time course of the C_e of both Pmab and Cmab is shown in Figure **5**.

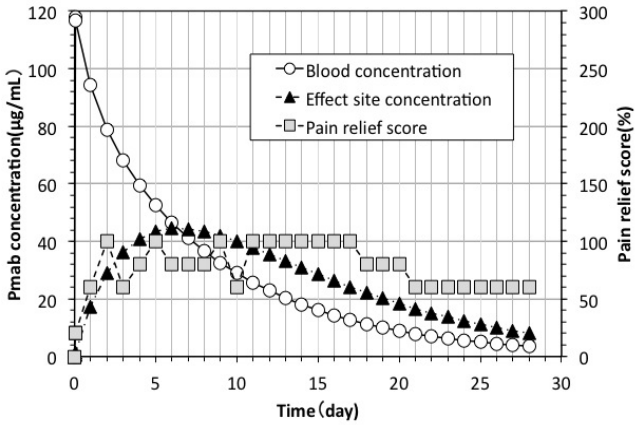

Figure 3: Time course of the estimated blood, effect-site concentrations, and pain relief score after intravenous administration of Pmab.

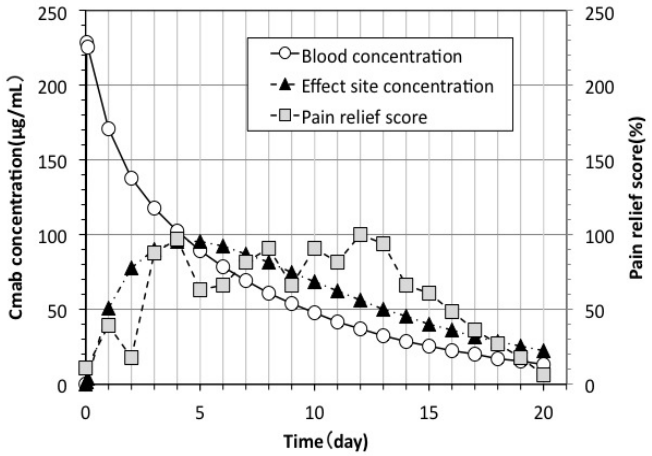

Figure 4: Time course of the estimated blood, effect-site concentrations, and pain relief scores after intravenous administration of Cmab.

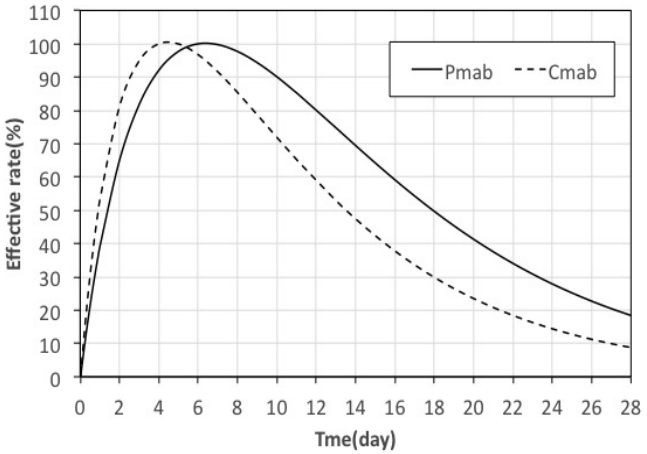

Figure 5: Time course of the estimated effective rate following intravenous administration of Pmab and Cmab.

DISCUSSION

In the present study PK/ PD simulations were performed to predict the Ce following intravenous infusion of Pmab and Cmab. The relationship between blood concentration and the analgesic effects of Pmab and Cmab, when administered intravenously over 1h. was found to exhibit counterclockwise progression of the effect relative to the changes in blood concentration when these agents were intravenously administered for 1h. This relationship can be adequately explained using the compartmental pharmacological model applied to previously published data.

The change in Pmab Ce was estimated using data from a previous report [1], describing change in NRS values of nociceptive pain after Pmab administration. The estimated duration of effect, defined as five times the calculated $t_{1/2}k_{e0}$ was 18.8 days, which closely approximated the 17-21 days duration of analgesic effect on neuropathic pain reported elsewhere [12]. This similarity suggests that the durations of analgesia for nociceptive and neuropathic pain are comparable. For Cmab, the k_{e0} was calculated using the difference in NRS scores between the placebo and treatment groups, because a placebo-controlled comparison was available, whereas no placebo-controlled data were available for Pmab. Despite this methodological discrepancy, minimal differences were observed between the ke0 value obtained from the placebo-corrected Cmab data and that from the Cmab treatment group alone. However, this asymmetrical data background represents a critical confounding factor in our direct comparison. While our sensitivity analysis for Cmab suggests that the estimation of the equilibration rate constant (k_{e0}) may be relatively robust against placebo effects, several inherent limitations of the present study must be explicitly and prominently acknowledged. First, this research relies entirely on the secondary analysis of previously published, digitized clinical plot data, which inherently restricts our ability to account for individual patient-level pharmacological variability, granular demographic distributions, or clinical co-medications. Second, a critical methodological limitation arises from the asymmetrical data background between the two agents; specifically, there is a complete lack of placebo-controlled pain intensity data for Pmab, whereas a robust placebo baseline was available for Cmab. The absolute NRS values used for Pmab cannot completely isolate the true, drug-specific pharmacological effect from potential placebo responses or background chronological noise in clinical pain perception. Therefore, the Pmab modeling results must be interpreted with caution. To minimize these clinical uncertainties, future prospective trials evaluating the PK/PD of anti-EGFR antibody analgesia should ideally incorporate standardized, placebo-controlled designs for all agents being compared.

In contrast, the estimated duration of effect for Cmab (five times its calculated $t_{1/2}k_{e0}$) was 11.3 days, closely matching the 12–day duration of sustained analgesic effect on neuropathic pain reported elsewhere [2]. Cmab is typically administered on either a 7-day or 14-day cycle. A sustained analgesic effect would therefore be expected with the 7-day dosing interval, whereas pain may recur shortly before the next scheduled dose under the 14-day interval. Collectively, these findings allowed us to explain the analgesic effects of Pmab and Cmab following intravenous administration using a compartmental pharmacological model, analogous to those previously applied to other classes of agents including analgesics [12, 15-20], neuromuscular blocking agents [18-19], and sedatives [16, 17].

The present study investigated the duration of the analgesic effects of Pmab and Cmab using the compartmental pharmacological model. It is also worth noting that EGFR inhibition by the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib relieves neuropathic pain [2, 25]. However, extrapolating the five-half-life convention to small-molecule TKIs is highly speculative given their profound physiological differences in molecular weight, pharmacokinetics, and tissue distribution. Consequently, this discussion is framed strictly as a hypothesis requiring prospective validation.

CONCLUSION

In conclusion, the compartmental pharmacological model can be used to predict the duration of the analgesic effects of EGFR inhibitors.

AUTHOR'S CONTRIBUTIONS

Conceptualization, S.Y., K.I., and Y.O.; methodology, S.Y, M.K., and C.O.; formal analysis, S.Y. and M.K.; data curation, S.Y., M.K, Y.T., Y.M., and S.K..; investigation, S.Y., R.H., A.A., S.H., Y.T., Y.M., C.T., and K.I.; writing-original draft presentation, S.Y., M.K, C.O., Y.T., Y.M., and K.I.; writing-review and editing, R.H., A.A., S.H., C.T., S.K., and Y.O. All authors approved the manuscript to be published, and agree to be accountable for all aspects of the work in

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING STATEMENT

This study received no external funding.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in compliance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and approved by the Ethics Committee of Nagoya Memorial Hospital (2014-#005; December 4, 2014).

INFORMED CONSENT STATEMENT

Information about study inclusion was posted on the hospital's homepage, and consent was obtained from each patient using an opt-out method.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this study are available from S.Y. and K.I. upon reasonable request.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the research, authorship, or publication of this manuscript.

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