Pharmacodynamic Analysis of Analgesic Clinical Trials Using Empirical Methods

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Data from analgesic clinical trials have characteristics such as ordered categorical longitudinal responses with repeated measures, delay of effect with respect to analgesic plasma concentration, and right-hand censoring of response due to remedication. In order to determine the concentration-effect relationship of such data, we propose convolving an empirical function for plasma concentration, in the form of broken lines which connect each pair of neighboring observations, with a monoexponential function, to generate "effect site concentration." Effect site concentration and time are used, simultaneously, as independent variables in the fit of the model for the logit of the probability of having a specific pain relief (PR) score at each time point pre-remedication, via maximum likelihood. Using corresponding effect site concentration, the probabilities of having specific PR scores post-remedication are predicted via the concentration-response relationship established. The overall (pre- and post-remedication) predictions and corresponding standard errors for the responses are then estimated. Inference of the PR scoring, using a posterior method, is proposed. An illustration using real data is used to demonstrate these methods.

KEY WORDS: analgesic; clinical trial methods; population pharmacodynamics; mixed effects models; empirical convolution.

INTRODUCTION

This paper addresses the analysis of analgesic clinical trial data, which have the following features: (i) the response, level of pain or pain relief, is an ordered categorical variable; (ii) the response is longitudinal and consists of repeated subjective measurements; (iii) response and plasma drug concentrations are observed according to the same sampling schedule and a delay between plasma concentration and effect exists; (iv) the response data are right-hand censored due to remedication (by a known analgesic other than the one under investigation); and (v) plasma drug concentrations are not censored. An introduction to analgesic clinical trials can be found in proceedings edited by Max, Portenov and Laska (1). Recently, Sheiner (2) proposed a new analysis method, appropriate for such data, to estimate the conditional probability distribution of having a specific pain relief (PR) score, as well as to estimate the conditional hazard of a discrete-valued survival time. He suggests that the fitted models can be used to predict the unconditional probability distribution using Monte Carlo simulation. As Sheiner points out, this information allows one to test efficacy, and to obtain predictions of response given dose and time, both of which are required for regulatory purposes and for optimal drug usage.

In this paper, we adopt Sheiner's general approach, and introduce several new aspects to provide researchers some alternatives. First, we introduce a new model-independent method, "empirical convolution," for generating "effect site concentration," $Ce(t)$. This procedure is not specific, per se, to the data described above, but was used in our analysis. Second, by assuming that within an individual the concentration-response relationship post-remedication is consistent with that prior to remedication, we introduce a method, which does not require hazard for the time of remedication, of estimating the overall predictions of PR score (given dose and time) with corresponding standard errors. These standard errors enables comparisons of responses to be made. Finally, we use posterior inference to rationalize the PR scoring and the proposed estimation to assure the data-based outcomes. This paper provides details of the methodology, and gives an illustration of its application.

METHODOLOGY

For non-steady-state pharmacodynamic data, drug effect, $Y(t)$, is often observed to be delayed with respect to simultaneous drug concentration in (usually venous) plasma, $C(t)$. Convolving $C(t)$ with $\exp(-k_{eo}t)$ to generate $Ce(t)$ is a widely accepted device to model such delays. Instead of modeling $C(t)$ parametrically, however, a semiparametric method is employed to implement the convolution. This submodel is then fitted simultaneously with the entire pharmacodynamic model.

First, we use broken lines which connect each pair of neighboring observations to express the function for plasma concentration, $C(t)$. If the k-th sample time, $k=1, 2, \cdots, K_{ij}$, in the i-th individual, $i=1, 2, \cdots, I_j$, of the j-th dose-level, $j=1, 2, \cdots, J$, is assigned to be t_{ijk} with $t_{ij0}=0$, the k-th observed plasma concentration in the i-th individual at the j-th dose-level is $C_{ijk}=C_{ij}(t_{ijk})$. One way to express the function $C_{ij}(t)$ is written as follows:

$$C_{ij}(t) = \alpha_{ijk} + \beta_{ijk}t, \quad t_{ij(k-1)} \leq t \leq t_{ijk}, \tag{1}$$

in which

$$\beta_{ijk} = [C_{ij}(t_{ijk}) - C_{ij}(t_{ij(k-1)})]/[t_{ijk} - t_{ij(k-1)}], \tag{2}$$

$$\alpha_{ijk} = C_{ij}(t_{ijk}) - \beta_{ijk}t_{ijk}, \tag{3}$$

for $k = 1, 2, \cdots, K_{ij}$.

We then convolve $C(t)$ with a monoexponential function, $\exp(-k_{eo}t)$, to generate another function $Ce(t)$, the so-called "effect site concentration" [cf. Fuseau and Sheiner (3)]. We use the term "empirical convolution" to describe this process. The empirical convolution is carried out as follows:

$$Ce_{ij}(t) = k_{eo}\int_0^t C_{ij}(s)\exp[-k_{eo}(t-s)]ds$$

$$= \sum_{h=1}^{k}\{(\alpha_{ijh} - \alpha_{ij(h-1)})\{1 - \exp[-k_{eo}(t - t_{ij(h-1)})]\}$$

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Table I. Number of Individuals Evaluated After a Single Dose of the Analgesic and Prior to Remedication

Time (h)	Treatment			
	Placebo	1 unit	2 units	4 units
0.00	36	36	36	35
0.25	36	35	36	35
0.50	36	35	36	35
0.75	36	35	36	35
1.00	36	35	36	35
1.50	18	29	34	32
2.00	14	25	34	32
3.00	7	19	31	31
3.50	6	16	30	28
4.00	6	12	26	24
5.00	6	11	24	18
6.00	6	11	20	17

$$+ [\beta_{ijh} - \beta_{ij(h-1)}]\{k_{eo}t - 1 - (k_{eo}t_{ij(h-1)} - 1) \exp[-k_{eo}(t - t_{ij(h-1)})]\}/k_{eo}\}, \quad (4)$$

for $t_{ij(k-1)} \leq t \leq t_{ijk}$, in which $\alpha_0 = \beta_0 = 0$, and k_{eo} is the effect site rate constant.

A logistic model [cf. Sheiner (2)], $\text{logit}(F(y_{ijk})) = g(y_{ijk}; \theta, \eta)$, is used to estimate the cumulative distribution function (F), in which Y_{ijk} is the variable PR score in the i-th individual of the j-th dose-level at the k-th time point, and y_{ijk} is its realization. The logit is associated with the parameter vector θ. The elements of interindividual variability are associated with the normally distributed vector η.

Expressed mathematically, the cumulative probability function is

$$F(y_{ijk}; \theta, \eta) = \Pr(Y_{ijk} < y_{ijk}; \theta, \eta) = \exp[g(y_{ijk}; \theta, \eta)]/\{1 + \exp[g(y_{ijk}; \theta, \eta)]\}, \quad (5)$$

$y_{ijk} = 0, 1, 2, 3, 4$, for which

$$\Pr(Y_{ijk} < 0; \theta, \eta) = 0, \quad (6)$$

and

$$\Pr(Y_{ijk} < 5; \theta, \eta) = 1. \quad (7)$$

In Eq. (5), we define

$$g(y_{ijk}; \theta, \eta) = \sum_{m=1}^{4} \theta_m Q_m(y_{ijk}) + \theta_5 \frac{t_{ijk}}{t_{ijk} + \theta_6} + \theta_7 \frac{Ce_{ijk}}{Ce_{ijk} + \theta_8} + \eta_{ij}, \quad (8)$$

in which $\theta = (k_{eo}, \theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \theta_6, \theta_7, \theta_8)'$, $\eta = (\eta_{11}, \cdots, \eta_{I_1 1}, \cdots, \eta_{1J}, \cdots, \eta_{I_J J})'$, and the indicator function $Q_m(y_{ijk})$, $m = 1, 2, 3, 4$, is defined as follows:

$$Q_m(y_{ijk}) = \begin{cases} 1, & y_{ijk} \geq m - 1, \\ 0, & \text{otherwise.} \end{cases} \quad (9)$$

Thus, the probability of having a specific PR score is

$$\Pr(Y_{ijk} = y_{ijk}; \theta, \eta) = \Pr(Y_{ijk} < y_{ijk} + 1; \theta, \eta) - \Pr(Y_{ijk} < y_{ijk}; \theta, \eta). \quad (10)$$

Note that Eqs. (4–10) with the constraint of $Ce(t) = 0$ for all t is the model for the placebo data. The component $\theta_5 t_{ijk}/(t_{ijk} + \theta_6)$ produces a monotonic and saturable placebo effect with respect to time [cf. Liu and Sambol (5)]. The component $\theta_7 Ce_{ijk}/(Ce_{ijk} + \theta_8)$ is the contribution of concentration to the logit, and also produces a monotonic and saturable (pure) drug effect with respect to Ce_{ijk}.

Given the definition of the logit in equation (8), the probability of having the observed PR scores at distinct times are

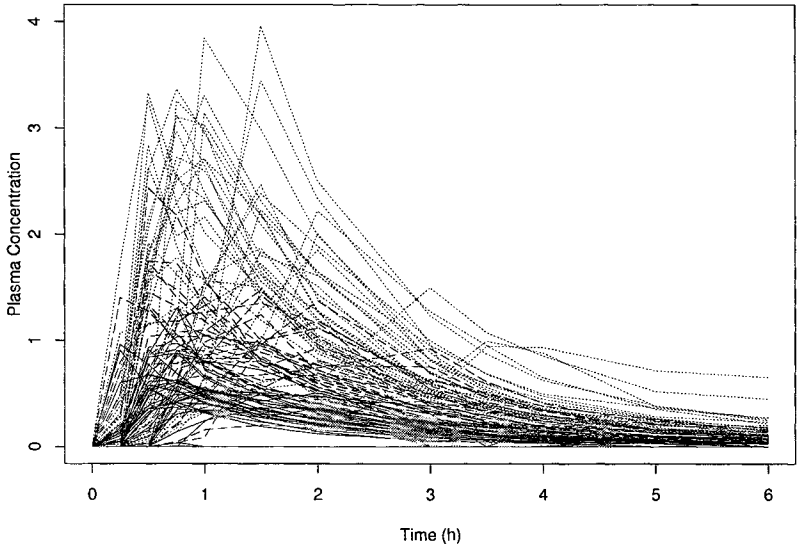

Fig. 1. Individual plasma concentration versus time curves among different dose groups. The *solid* lines indicate the plasma concentration-time curves for individual subjects who received a 1 unit dose; the *dashed* lines are the plasma concentration-time curves for subjects who received a 2 unit dose; and the *dotted* lines belong to subjects who received a 4 unit dose.

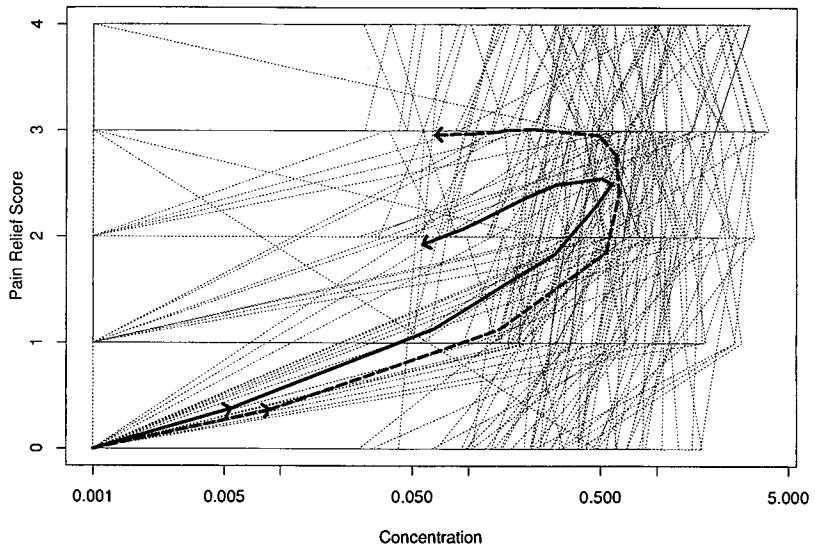

Fig. 2. Observed pain relief score versus concentration. The *dotted thin* lines are the observed pain relief score versus plasma concentration curves, in the order of observation times, for individual subjects. The *dashed thick* line indicates the mean pain relief score-mean plasma concentration curve. The *solid thick* line indicates the mean pain relief score versus mean 'effect site' concentration curve. Arrows indicate the order of observation times. Hysteresis seen with the observed pain relief score-plasma concentration curves is partially corrected in the pain relief score versus 'effect site' concentration curve. The lack of complete collapse is expected, and may be due to the censorship and an increasing time effect, as a part of the placebo effect, which has not been subtracted from the curve.

independent. Thus, the likelihood function of the data can be written as follows:

$$L(\theta, \eta) = \prod_{i,j,k} l_{ijk}, \tag{11}$$

in which $l_{ijk} = \Pr(\theta, \eta; Y_{ijk} = y^*_{ijk})$ and y^*_{ijk} is the observed PR score (pre-remedication). A nonlinear mixed effect model, employing the software NONMEM, Laplacian method [see Beal and Sheiner (4)], is used to minimize $-2 \sum_{i,j,k} \log(l_{ijk})$.

Based on the maximum likelihood estimates ($\hat{k}_{eo}$, $\hat{\theta}$ and $\hat{\eta}$), the first two moments of the empirical distribution of the PR score [prediction (mean), $\hat{Y}_{ijk}$, and variance, $\hat{V}_{ijk}$) can be obtained using Eqs. (12–13):

$$\hat{Y}_{ijk} = \sum_{h=0}^{4} h \Pr(Y_{ijk} = h; \hat{\theta}, \hat{\eta}_{ij}); \tag{12}$$

$$\hat{V}_{ijk} = \sum_{h=0}^{4} [h - \hat{Y}_{ijk}]^2 \Pr(Y_{ijk} = h; \hat{\theta}, \hat{\eta}_{ij}). \tag{13}$$

Assuming that within an individual the concentration-response relationship post-remedication does not differ significantly from pre-remedication, the probabilities of having specific PR scores post-remedication can be obtained from Eqs. (4–10). The PR scores post-remedication can then be predicted from the post-remedication probabilities using Eq. (13).

The prediction and variance of the PR score for each treatment can be obtained using Eqs. (14–15), respectively:

$$\hat{Y}_{jk} = \frac{1}{I_j} \sum_{i=1}^{I_j} \hat{Y}_{ijk}; \tag{14}$$

$$\hat{V}_{jk} = \frac{1}{I_j} \sum_{i=1}^{I_j} (\hat{Y}_{ijk} - \hat{Y}_{jk})^2. \tag{15}$$

The (pure) drug effect and corresponding variance can be estimated using Eqs. (16–17), respectively:

$$\hat{Y}_{jk}(\text{drug}) = \hat{Y}_{jk} - \hat{Y}_k(\text{placebo}); \tag{16}$$

$$\hat{V}_{jk}(\text{drug}) = \hat{V}_{jk} + \hat{V}_k(\text{placebo}). \tag{17}$$

Because PR scoring is an artificial system (i.e., one may choose any ordinal scores instead of the present scores), we use the term "prediction" instead of "expectation" for the first moment. Further, given the present artificial PR scoring system of 0, 1, 2, 3, and 4, it is desirable to know whether the pre-remedication predictions match the observed PR scores. Note that post-remedication predictions do not have corresponding observations. To rationalize the scoring system, with respect to the proposed estimation, we suggest using

Table II. Parameter Estimates

Parameter	Estimate	Parameter	Estimate
k_{eo} (h^{-1})	3.03	σ_η	8.40
θ_1	8.47	θ_5	−5.96
θ_2	2.47	θ_6 (h)	0.55
θ_3	1.42	θ_7	−8.75
θ_4	2.82	θ_8 (ng/ml)	945

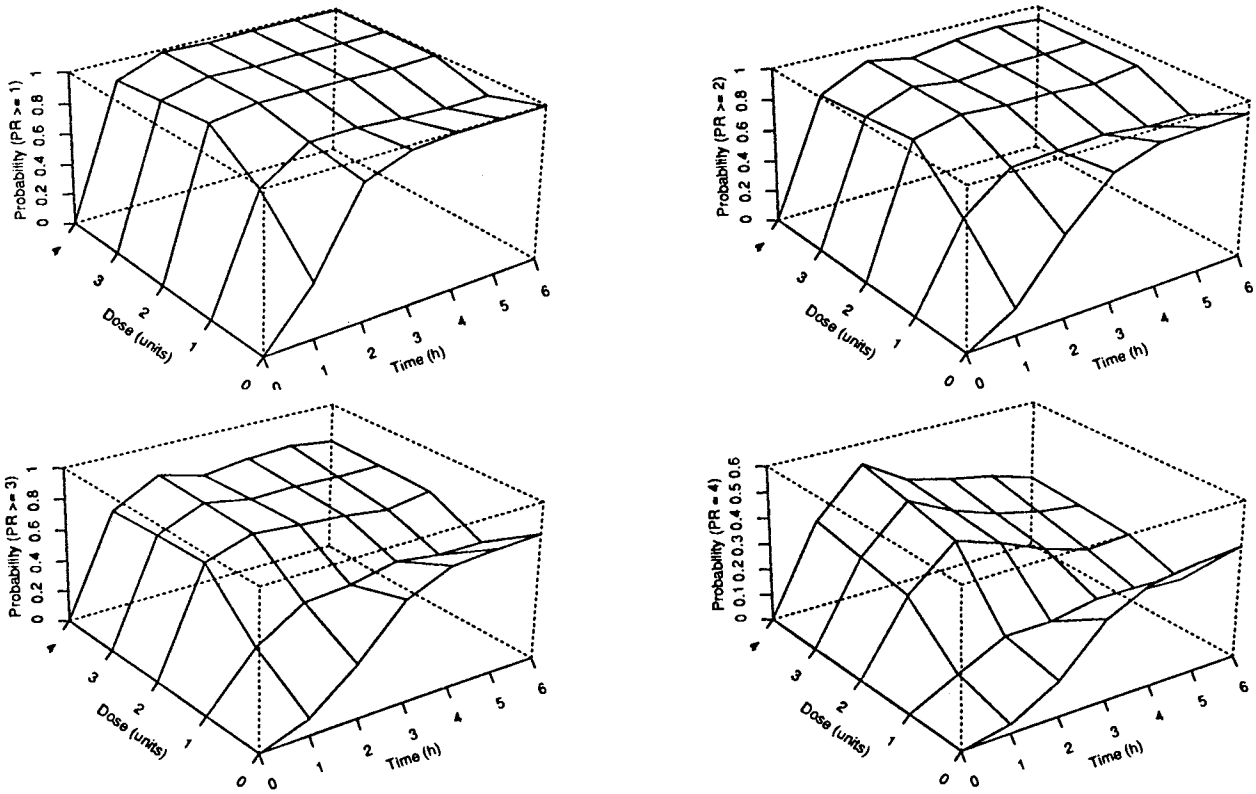

Fig. 3. Pre-remedication probability (z-axis) of having specific pain relief scores as a function of time (x-axis) and dose (y-axis). **Upper left panel:** pain relief score = 1, **upper right panel:** pain relief score = 2, **lower left panel:** pain relief score = 3, and **lower right panel:** pain relief = 4. Censoring, due to remedication, makes surfaces rise and fall, particularly with respect to placebo and at later times where dropouts are more prevalent.

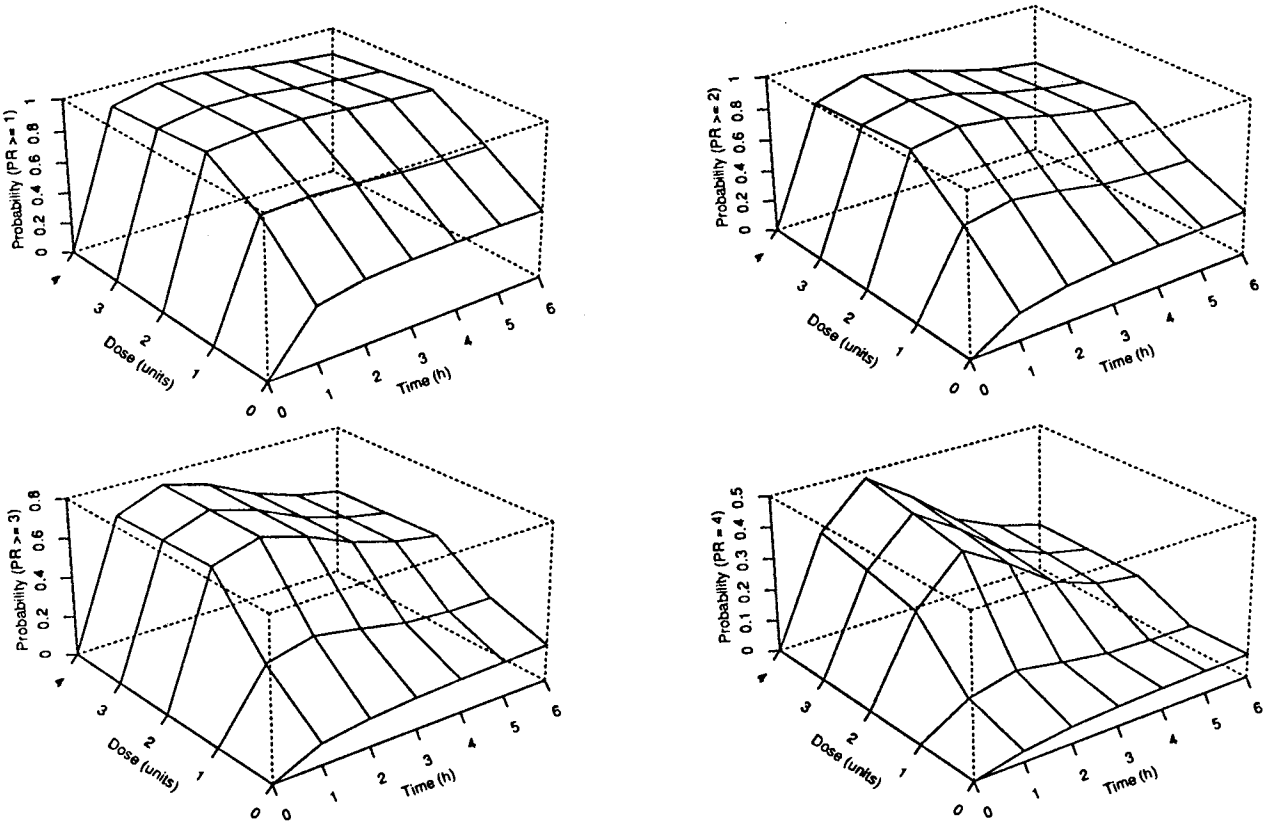

Fig. 4. Overall (pre- and post-remedication) probability (z-axis) of having specific pain relief scores as a function of time (x-axis) and dose (y-axis). **Upper left panel:** pain relief score = 1, **upper right panel:** pain relief score = 2, **lower left panel:** pain relief score = 3, and **lower right panel:** pain relief score = 4.

Table III. Observed and Predicted PR Scores After a Single Dose of the Analgesic and Prior to Remedication

Dose Level		Time (*h*)										
		0.25	0.50	0.75	1.00	1.50	2.00	3.00	3.50	4.00	5.00	6.00
	n*	36	36	36	36	18	14	7	6	6	6	6
Placebo	Observed	0.17	0.42	0.72	0.72	1.50	1.71	3.00	3.50	3.50	3.50	3.33
	s.e.†	0.09	0.14	0.16	0.16	0.29	0.38	0.47	0.24	0.24	0.24	0.37
	Predicted	0.36	0.50	0.60	0.67	1.53	1.87	2.76	3.04	3.07	3.12	3.15
	s.e.	0.12	0.14	0.16	0.17	0.25	0.29	0.38	0.32	0.31	0.31	0.30
	n*	35	35	35	35	29	25	19	16	12	11	11
1 unit	Observed	0.26	0.80	1.77	1.77	2.52	2.56	2.47	2.56	2.50	2.45	2.36
	s.e.	0.10	0.18	0.22	0.22	0.23	0.26	0.32	0.36	0.44	0.41	0.45
	Predicted	0.42	0.93	1.40	1.67	2.22	2.38	2.43	2.42	2.51	2.40	2.39
	s.e.	0.09	0.14	0.18	0.20	0.18	0.19	0.21	0.24	0.31	0.33	0.33
	n*	36	36	36	35	34	34	31	30	26	24	20
2 units	Observed	0.47	1.11	2.44	2.51	3.00	3.21	3.06	2.97	3.27	3.08	3.10
	s.e.	0.14	0.18	0.18	0.17	0.15	0.14	0.16	0.23	0.17	0.21	0.16
	Predicted	0.48	1.41	2.18	2.61	3.09	3.08	2.97	2.82	2.88	2.76	2.87
	s.e.	0.11	0.16	0.18	0.16	0.13	0.13	0.14	0.15	0.14	0.15	0.12
	n*	35	35	35	35	32	32	31	28	24	18	17
4 units	Observed	0.51	1.49	2.49	2.49	3.06	3.25	3.13	3.11	3.21	3.22	3.18
	s.e.	0.15	0.21	0.22	0.22	0.18	0.14	0.20	0.22	0.20	0.20	0.20
	Predicted	0.59	1.44	2.20	2.71	3.18	3.22	2.97	2.95	3.03	3.05	2.94
	s.e.	0.11	0.19	0.21	0.21	0.16	0.14	0.16	0.16	0.14	0.13	0.14

n*: number of individuals under observation.
s.e.†: standard error.

normal-based tests (note that in analgesic clinical trials the total number of observed PR scores which are equal to a given score is usually large) with the null hypothesis $H_0: E(\hat{Y}_{ijk} | y^*_{ijk} = m) - m = 0$, and the following posterior mean and standard error [cf. Tanner (6) and Geweke (7)]:

$$\hat{E}(\hat{Y}_{ijk} \mid y^*_{ijk} = m) = \Sigma(\hat{Y}_{ijk} \mid y^*_{ijk} = m) l_{ijk} / \Sigma l_{ijk} \quad (18)$$

and

$$\text{s.e.}(\hat{Y}_{ijk} \mid y^*_{ijk} = m) = \sqrt{\Sigma[(\hat{Y}_{ijk} \mid y^*_{ijk} = m) - \hat{E}(\hat{Y}_{ijk} \mid y^*_{ijk} = m)]^2 \cdot l^2_{ijk} / \Sigma l_{ijk}}, \quad (19)$$

in which $m = 0, 1, 2, 3, 4$.

ILLUSTRATION

A study of an investigational analgesic agent included 143 individuals randomized to one of three active treatments or placebo. Table I lists the number of subjects who were evaluated prior to remedication in each treatment.

Twelve-hundred and ten plasma concentrations collected during the three active treatments are shown in Fig. 1. The observed PR score versus plasma concentration at each time point, pre-remedication only, is shown in Fig. 2. Note the counter-clockwise hysteresis indicating delay between plasma concentration and effect.

Table II provides the mean estimates of the parameters, based on 1,134 pre-remedication effect observations, including 207 placebo observations.

As one might expect, the predicted cumulative proba-

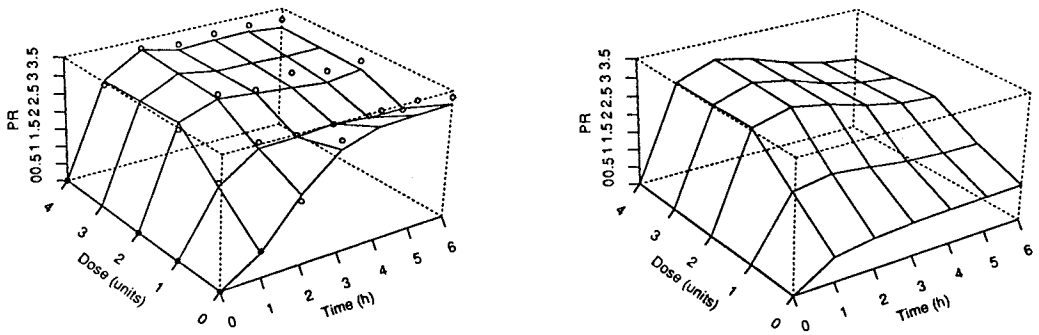

Fig. 5. Predicted pain relief score (*z*-axis) as a function of time (*x*-axis) and dose (*y*-axis), prior to remedication **(left panel)**. The circles show corresponding mean observations. Censoring, due to remedication, makes the surface rise and fall, particularly with respect to placebo and at later times where dropouts were more prevalent. The **right panel** shows the comparable predictions overall (pre- and post-remedication).

Table IV. Overall (Pre- and Post-Remedication) Predicted PR Scores After a Single Dose of the Analgesic

Dose Level		Time (*h*)										
		0.25	0.50	0.75	1.00	1.50	2.00	3.00	3.50	4.00	5.00	6.00
	n*	36	36	36	36	36	36	36	36	36	36	36
Placebo	Predicted	0.36	0.50	0.60	0.67	0.77	0.83	0.90	0.92	0.94	0.97	0.98
	s.e.†	0.12	0.14	0.16	0.17	0.18	0.19	0.20	0.20	0.20	0.20	0.21
	n*	35	35	35	35	35	35	35	35	35	35	35
1 unit	Predicted	0.41	0.90	1.36	1.63	1.81	1.81	1.69	1.61	1.55	1.49	1.47
	s.e.	0.09	0.14	0.18	0.20	0.21	0.21	0.20	0.20	0.19	0.19	0.19
	n*	36	36	36	36	36	36	36	36	36	36	36
2 units	Predicted	0.48	1.41	2.18	2.61	2.93	2.93	2.74	2.59	2.43	2.19	2.04
	s.e.	0.11	0.16	0.18	0.17	0.16	0.17	0.16	0.16	0.16	0.17	0.17
	n*	35	35	35	35	35	35	35	35	35	35	35
4 units	Predicted	0.59	1.44	2.20	2.64	2.94	3.00	2.78	2.60	2.45	2.26	2.15
	s.e.	0.11	0.19	0.21	0.21	0.20	0.18	0.19	0.19	0.20	0.20	0.20

n*: number of individuals under observation.
s.e.†: standard error.

bility of having positive PR scores in association with pre-remedication (Fig. 3) is greater than that which would be predicted if all patients continued to be observed (Fig. 4). This observation is particularly evident at later times, and in the placebo group, where dropouts are more prevalent.

Table III lists the observed and predicted PR scores pre-remedication, and the left panel of Fig. 5 shows the predictions of the model relative to the data. The overall (pre- and post-remedication) predictions are listed in Table VI, and the right panel of Fig. 5 shows the overall response surface.

Fig. 6 shows the (pure) drug effect based on the outcomes listed in Table IV. It is apparent that the drug effect of 1 unit is greater than the placebo effect, and the drug effect of 2 or 4 units is greater than that of 1 unit. The drug effect of 4 units could not, however, be distinguished from that of 2 units.

To judge the PR scoring, Table V shows the posterior arguments obtained using Eqs. (19–20). Using proposed approach, generally speaking, PR scores lower than 2 would be slightly overestimated, and those higher than 2 would be slightly underestimated. Inferenced by its standard error, the difference between any given PR scores and corresponding posterior expectation was not statistically significant. Considering the complexity of analyzing analgesic clinical trials, those non-significantly shifted $\hat{E}(\hat{Y}_{ijk}|y^*_{ijk}=m)$ suggest that both the scoring system and the proposed methods are reasonable.

DISCUSSION

The first new aspect we introduced in the paper, empirical convolution, can be a useful tool in pharmacodynamic studies. It is an informative optimization due to the fact that it depends on observed concentrations without any transfor-

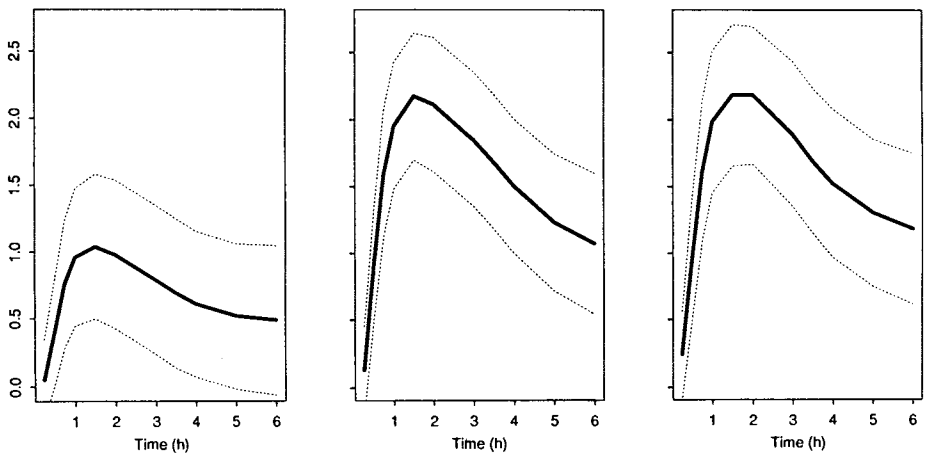

Fig. 6. Predicted (*solid line*) and 95% confidence region (bounded by *dashed lines*) of pure drug effect, the difference between the effect of active treatment and that of placebo treatment, versus time. **Left panel:** 1 unit dose, **middle panel:** 2 unit dose, and **right panel:** 4 unit dose. As can be seen by comparing mean response and confidence bounds, the responses of the lowest dose (at comparable time points) differ significantly from those of the other two doses, but the two higher doses do not differ significantly from each other.

Table V. Posterior Arguments for PR Scoring Sample Size, Posterior Mean, and Standard Error

Argument	m				
	0	1	2	3	4
n_m	267	160	148	327	232
$\hat{E}(\hat{Y}_{ijk} \mid y^*_{ijk} = m)$	0.120	1.172	1.981	2.835	3.691
s.e.$(\hat{Y}_{ijk} \mid y^*_{ijk} = m)$	0.163	0.296	0.214	0.294	0.264

mation. It is particularly useful when the convolution can not be carried out in a conventional way without an explicit function (e.g., a compartmental model) to describe the plasma concentration-time relationship, for example, when the plasma concentration-time profile is erratic (i.e., multiple peaks). However, if the sampling schedule is such that neighboring concentrations are too far apart in a critical region (e.g., before and after the peak), the empirical convolution may carry significant biases.

As mentioned in the introduction, we focused our investigation on data in which observed plasma concentrations are not censored. Because of the local, rather than global, nature of empirical convolution, this approach would not be appropriate when *both* plasma concentration and response are right-hand censored due to remedication. In this case, an alternative is using empirical convolution based on uncensored data for obtaining $Ce(t)$ pre-remedication, and then modeling $Ce(t)$, which is smoother than observed $C(t)$, with a global approach (e.g., a Bateman function) to obtain predictions at time points post-remedication. We have had some experience using this technique on analgesic data which involved erratic concentrations and censoring of both concentration and response, and achieved reasonable results.

The logit we used in this paper, Eq. (8), includes a saturable contribution of time and another for Ce. A general form of a logit for analyzing analgesic clinical trials is $\sum_{m=1}^{n-1}\theta_m Q_m(y) + f_1(t, \theta^{(0)}) + f_2(Ce(t), \theta^{(1)}) + \eta$, in which n is the number of response category, $\theta^{(0)}$, $\theta^{(1)}$ and η are vectors, $\sum_{m=1}^{n-1}\theta_m Q_m(y) + f_1(t, \theta^{(0)})$ determines the contribution to the logit from the placebo effect, $f_2(Ce(t), \theta^{(1)})$ determines that from the (pure) drug effect, and η represents interindividual variation. Different types of f_1 and f_2 should be considered for different types of data. We have used Emax (saturation)-type models for both f_1 and f_2 in our analysis. Because f_1 and f_2 are included in the logit, which has a similar (saturable) nature to it, other functions [such as a power function of t or $Ce(t)$] might be as good or better. We plan to investigate this aspect in our future work. In Sheiner's paper (2), variability depends on time. We suggest that the requirement for this dependence on time may be due, in-part, to misspecification of the placebo model. With finite values, according to Eqs. (5–10), any logit can not produce 100% probability for having a single PR score. Therefore, from Eq. (13), even though an observed PR score may be zero, the prediction will always be greater than zero. Likewise, the prediction will always be less than 4 for an observed PR score of 4. This fact may help to explain the slightly shifted, but not significantly biased, expectations shown in Table V.

Obtaining predictions for the placebo treatment is an important component of the overall estimation, as it provides us the information needed to evaluate pure drug effect. Although the censoring in response is informative, the large degree to which it occurs in the placebo group requires that sample size considerations for this group be conservative. For the example data in this paper, 6 of 36 placebo recipients completed all evaluations with coefficients of variation less than 30% at later times, and simultaneous modeling was able to be applied without a problem. In the case where placebo data does not support simultaneous modeling, a stepwise method, i.e., modeling the placebo effect first, then the active drug effect with the placebo parameter estimates fixed, is a reasonable approach.

Using the first two moments, predicted PR scores with corresponding standard errors for each dose group at each time point are obtainable. The importance of these predictions and standard errors lies in their ability to enable comparisons of response among different dose groups to be made, for example, to demonstrate drug efficacy and to make various claims (e.g., onset of action).

In summary, we have introduced several new aspects to modeling analgesic clinical trials. One aspect, the empirical convolution, has more general applicability to pharmacokinetic-pharmacodynamic data because it can also be used when the pharmacodynamic data are continuous. The other aspects have general applicability, but to data with ordered categorical response. Further, we have demonstrated that reasonable results may be achieved when using these techniques on real data.

APPENDIX

Empirical Convolution: From Integral to Summation

Let

$$C_{ij}(t) = \alpha_{ijk} + \beta_{ijk}t, \qquad t_{ij(k-1)} \leq t \leq t_{ijk} \tag{A.1}$$

be the plasma concentration in the i-th individual, $i = 1, 2, \cdots, I_j$, of the j-th dose level, $j = 1, 2, \cdots, J$, between the $(k-1)$-th and k-th sample time, $k = 1, 2, \cdots, K_{ij}$, with $t_{ij0} = 0$ and $\alpha_{ij0} = \beta_{ij0} = 0$, and

$$\phi_{ijk}(t) = \begin{cases} 0, & t \leq t_{ij(k-1)}, \\ [\alpha_{ijk} - \alpha_{ij(k-1)}] + [\beta_{ijk} - \beta_{ij(k-1)}]t, & t > t_{ij(k-1)}. \end{cases} \tag{A.2}$$

It yields the following function:

$$C_{ij}(t) = \sum_{h=1}^{k} \phi_{ijh}(t), \tag{A.3}$$

for $t_{ij(k-1)} \leq t < t_{ijk}$. Thus, we have the following convolution for $t_{ij(k-1)} \leq t < t_{ijk}$:

$$Ce_{ij}(t) = k_{eo} \int_0^t C_{ij}(s)\exp[-k_{eo}(t-s)]ds$$

$$= k_{eo} \int_0^t \sum_{h=1}^{k} \phi_{ijh}(s)\exp[-k_{eo}(t-s)]ds$$

$$= k_{eo} \sum_{h=1}^{k} \int_0^t \phi_{ijh}(s)\exp[-k_{eo}(t-s)]ds. \quad (A.4)$$

We also have the following results of integrals for $t_{ij(k-1)} \leq t < t_{ijk}$:

$$\int_0^t [\alpha_{ijh} - \alpha_{ij(h-1)}]\exp[-k_{eo}(t-s)]ds =$$

$$[\alpha_{ijh} - \alpha_{ij(h-1)}]\{1 - \exp[-k_{eo}(t - t_{ij(h-1)})]\}/k_{eo} \quad (A.5)$$

and

$$\int_0^t [\beta_{ijh} - \beta_{ij(h-1)}]t \exp[-k_{eo}(t-s)]ds =$$

$$[\beta_{ijh} - \beta_{ij(h-1)}]\{k_{eo}\, t - 1 - (k_{eo}\, t_{ij(h-1)} - 1)$$
$$\exp[-k_{eo}(t - t_{ij(h-1)})]\}/k_{eo}^2, \quad (A.6)$$

By inserting (A.5) and (A.6) to (A.4), for $t_{ij(k-1)} \leq y < t_{ijk}$, it yields the equation (4):

$$Ce_{ij}(t) = k_{eo} \int_0^t C_{ij}(s)\exp[-k_{eo}(t-s)]ds$$

$$= \sum_{h=1}^{k} \{[\alpha_{ijh} - \alpha_{ij(h-1)}]\{1 - \exp[-k_{eo}(t - t_{ij(h-1)})]\}$$

$$+ [\beta_{ijh} - \beta_{ij(h-1)}]\{k_{eo}\, t - 1 - (k_{eo}\, t_{ij(h-1)} - 1)$$
$$\exp[-k_{eo}(t - t_{ij(h-1)})]\}/k_{eo}\}. \quad (4)$$

Therefore, equation (4) is an exact expression of the convolution.

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