An Extension of the Indirect Response Models to Ordered Categorical Pharmacodynamic Data using Latent Variables

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ABSTRACT

BACKGROUND/AIMS: Indirect response models provide a semi-mechanistic framework to address drug-induced temporal delays in response-time profiles relative to drug exposure profiles. Currently, this methodology is developed for continuous response data only. No general theory exists for addressing drug-induced delay in ordered categorical response data. An extension of the indirect model methodology for ordered categorical data is proposed using the concept of a latent variable.

METHODS: The approach is motivated by the statistical concept of a latent variable – an underlying and unmeasurable continuous process (such as inflammation or disease state), which is mapped into the measurable ordered categorical data. The four indirect response mechanisms are applied to this latent variable to derive a set of indirect, latent variable response models (ILVRM).

RESULTS: Stochastic simulations were implemented to produce expected (mean) longitudinal response profiles, which are presented graphically for the four ILVRM as a function as a function of exposure (or dose) and time. Ultimately, the ILVRM simulation results characterize the drug-induced delay in effect, which can be used to discriminate between potential model types (a priori) when performing data analysis.

CONCLUSIONS: ILVRM methodology provides a natural (pharmacologically interpretable) way to extend indirect response mechanisms to ordered categorical data.

INTRODUCTION

Indirect response models (IRMs) provide a semi-mechanistic framework for linking pharmacodynamic (PD) responses to plasma concentrations (PK) and are useful when the PD and PK are not in equilibrium (the PD peaks or nadirs are not aligned temporally with Cmax). IRMs are well characterized in the literature.[1,2] In general, IRMs can be represented as

$$\frac{dR}{dt} = k_1 u(t) - k_2 v(t) R(t), \quad R(t=0) = \frac{k_1}{k_2} = R_o \qquad \text{Eq. (1)}$$

where k_1 is a zero-order production rate, k_2 is a first-order elimination rate, $u(t)$ and $v(t)$ are stimulatory or inhibitory forcing functions – ie,

$$u(t) \text{ or } v(t) = 1 \pm \frac{E\max \cdot C_p}{EC_{50} + C_p} \qquad \text{Eq. (2)}$$

and $R(t)$ is the model predicted response at time t. For continuous PD data, the statistical model for IRMs can be represented

$$y = R(t) + \varepsilon \qquad \text{Eq. (3)}$$

where y is the measured response and ε is the residual error. The population parameters of Eqs. (1)-(3) can be estimated using the ELS objective function of NONMEM.[3]

Sometimes efficacy and often safety data[‡] are measured as discrete, ordered categorical responses. Familiar examples are pain/pain relief, dizziness, and somnolence. Empirical models are often fit, ignoring the underlying pharmacological processes when formulating the functional forms of these generalized nonlinear models (logistic type). *Yet, the pharmacological processes that underpin these responses, do not change just because the response is discrete/ordered categorical (imprecise, quantal). The underlying drug mechanism (ie., binding to receptors, modulating cascades of events) is identical to that had the response data been continuous.*

Extension of IRMs to ordered categorical (OC) data is motivated here by the concept of a latent variable to yield indirect latent variable response models (ILVRM). An LV is an underlying, unobservable variable, that maps into OC responses by the probability mass between thresholds.[4,5] The concept can be likened to PK concentrations (the LV) reported as either above or below a quantification limit (the binary response). *The framework in Gibbons and Hedeker for (generalized) linear mixed effect LV models is also extended to (generalized) nonlinear mixed effect LV models.*[5]

The Method section contains a more mathematical development of the ILVRMs; the individual and marginal likelihoods for fitting the models; and the details of the simulation used to calculate the model predictions. The Results section displays the results of the simulation graphically. The Discussion section compares the ILVRM to the familiar OC data model for pain relief developed by Sheiner and Beal (and others), and is followed by a brief conclusion.

METHODS

Binary Responses (Probit Model)

The latent variable for ILVRM is defined here as

$$z_{ij}^* = R_{ij}(t)\exp(\sigma\varepsilon_{ij}) \qquad \text{Eq. (4)}$$

where z_{ij}^* is the continuous (unobservable) LV, $R_{ij}(t)$ is the model prediction of LV response (Eq. (1)), σ scales the residual variability, and ε_{ij} is (unobservable) error, $\varepsilon \sim N(0,1)$, all for individual i at the time j. The dependence of z^* on subject-specific random effects (η's in NONMEM) is suppressed for ease of exposition. The LV is assumed to be lognormal distributed (see below). Using the closed form solution of $R(t)$,

$$\begin{aligned} R(t) &= R_o \exp(-\phi(t))(k_2\xi(t)+1) = R_o\kappa(t) \\ \phi(t) &= k_2\int_0^t v(w)dw \\ \xi(t) &= \int_0^t \exp[\phi(w)]u(w)dw \end{aligned} \qquad \text{Eq. (5)}$$

(w is the integration variable) and applying the log-transform to both sides of Eq. (4) yields

$$\ln z_{ij}^* = z_{ij}^{**} = \ln R_{ij}(t) + \sigma\varepsilon_{ij} = \ln R_{o,i} + \ln\kappa_{ij}(t) + \sigma\varepsilon_{ij} \qquad \text{Eq. (6)}$$

Let z_{ij} be the observable binary response. Conceptually, $z_{ij} = 1$ when z_{ij}^{**} (or $\ln z_{ij}^*$) exceeds some threshold, γ. More precisely,

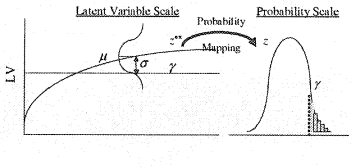
$$\begin{aligned} P(z_{ij}=1) &= P(z_{ij}^{**} > \gamma) = \frac{1}{\sqrt{2\pi\sigma^2}}\int_\gamma^\infty \exp\left[-\frac{(z_{ij}^{**} - \ln R_{ij})^2}{2\sigma^2}\right]dz^{**} \\ &\Phi[-(\gamma - \ln R_{ij})/\sigma] = \Phi(-q_{ij}) \end{aligned} \qquad \text{Eq. (7)}$$

where $\Phi(\bullet)$ is the cumulative normal distribution. Note that q_{ij}

$$q_{ij} = \frac{\gamma - \ln R_{o,i} - \ln\kappa_{ij}(t)}{\sigma} = \frac{\theta_i - \ln\kappa_{ij}(t)}{\sigma} \qquad \text{Eq. (8)}$$

which indicates the estimates of $R_{o,i}$ and γ are not unique (thus, γ can be arbitrarily set to 0 without loss of generality).[‡] Note that unlike the linear case where σ is unidentifiable and set to 1, σ can be estimated (ln $\kappa_{ij}(t)$ is not modified by a parameter) and its inclusion is necessary for correct estimates of k_2.

The mapping of the LV to the probability scale for fitting OC data can be related pictorially



The marginal likelihood for individual i is constructed as

$$l(\mathbf{z}_i|\boldsymbol{\eta}_i) = \prod_{j=1}^{n_i}[\Phi(-q_{ij})]^{z_{ij}}[1-\Phi(-q_{ij})]^{1-z_{ij}} \qquad \text{Eq. (9)}$$

which assumes independent observations within a subject. Assuming $\boldsymbol{\eta} \sim h(\bullet) \equiv N(\mathbf{0},\boldsymbol{\Omega})$, the Laplace approximation can be used to approximate the integral for the marginal likelihood,

$$L(\mathbf{z}_i) = \int_{\boldsymbol{\eta}} l(\mathbf{z}_i|\boldsymbol{\eta}_i)h(\boldsymbol{\eta})d\boldsymbol{\eta} \qquad \text{Eq. (10)}$$

facilitating estimation using NONMEM.[3]

Ordered Categorical Responses (Ordinal)

For K levels, there are $K+1$ thresholds, where $\gamma_0 < \gamma_1 < \ldots < \gamma_{K-1} < \gamma_K$, with $\gamma_0 = -\infty$ and $\gamma_K = \infty$. The probability for response k is

$$\begin{aligned} P(z_{ij}=k) &= P(\gamma_{k-1} > z_{ij}^{**} \geq \gamma_k)] \\ &= \Phi[-(\gamma_k - \ln R_{ij})/\sigma] - \Phi[-(\gamma_{k-1} - \ln R_{ij})/\sigma] \end{aligned} \qquad \text{Eq. (11)}$$

As above, $\gamma_1 \equiv 0$ without loss of generality. The individual and marginal likelihoods can be constructed in a similar fashion as the binary response case.

Logistic Model for Binary Responses

The logistic framework for the binary response case is defined

$$P(z_{ij}=1) = P(z_{ij}^{**} > \gamma) = \Psi(q_{ij}') = [1+\exp(q_{ij}')]^{-1} \qquad \text{Eq. (12)}$$

Where $\Psi(\bullet)$ is the familiar logistic function. Note that the logistic density (not shown) has a mean of 0, a variance of $\pi^2/3$, and is similar to the t-distribution with 9 df. Extension to ordered categorical data is similar to the normal (probit) case.

Simulation

Simulations for the binary response probit model were conducted based on

METHODS (CONTINUED)

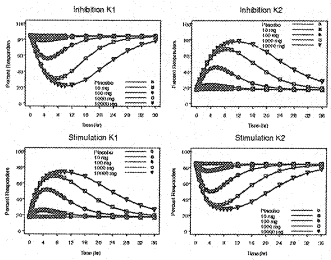
Methylprednisolone kinetic parameters, used initially to characterize the four IRMs.[2] Lognormal interindividual variability was added to generate population characteristics. The PK model was simulated with CL_i=27 L/hr, V_c=90 L, (k_e=0.3 hr^{-1}), Var($\eta^{(CL_i)}, \eta^{(V)}$)= Diag[0.04,0.09] at doses 0,10,100,1000,10000. For the ILVRM, the four IRMs were simulated using Eqs. (1)-(2) with $k_1 = 9$ units/hr, $k_2 = 0.3$ hr^{-1}, ($R_o = 30$ units), $EC_{50} = 250$ ng/mL, Emax = 0.6 for inhibitory and 1.0 for stimulatory models, and Var($\eta^{(k1)}, \eta^{(k2)}, \eta^{(EC50)}, \eta^{(Emax1)}$) = Diag[0.09,0.04,0.04,0.09]. Also, $\gamma \equiv 3$ or 3.8 (to keep original R_o) and $\sigma \equiv 0.2$. Model predictions (marginal expectations or population means) were calculated using the sample mean Monte Carlo method

$$\begin{aligned} E(\mathbf{z}_{ij}) &= \int_{\boldsymbol{\eta}} E(\mathbf{z}_{ij}|\boldsymbol{\eta}_i)h(\boldsymbol{\eta})d\boldsymbol{\eta} = \int_{\boldsymbol{\eta}} \Phi(-q_{ij}|\boldsymbol{\eta}_i)h(\boldsymbol{\eta})d\boldsymbol{\eta} \\ &\sim \frac{1}{M}\sum_{i=1}^{M}\Phi(-q_{ij}|\boldsymbol{\eta}_i^*) = \frac{1}{M}\sum_{i=1}^{M}P(z_{ij}=1|\boldsymbol{\eta}_i^*) \end{aligned} \qquad \text{Eq. (13)}$$

where $\boldsymbol{\eta}^*$, is sampled from $h(\bullet) \equiv N(\mathbf{0},\boldsymbol{\Omega})$. Simulations were performed using NONMEM V with M=1000. $\Phi(\bullet)$ was approximated using the method of Abramowitz and Stegun.[6,‡]

RESULTS

As with IRMs for continuous PD data, the PD nadirs and peaks for ILVRMs also depend upon the dose (concentration profile).



DISCUSSION

Formulating the ILVRMs on an additive error scale (not log) with a placebo effect, $f_p(t)$, under stimulatory $u(t)$ (Eq. (2)), and collapsing the model (as in Hutmacher, *et. al.*, $k_1 \to \infty, k_2 \to \infty, k_1/k_2 \to R_o$),

$$\begin{aligned} q &= R_o\kappa(t) + f_p(t) - \gamma \to R_o u(t) + f_p(t) - \gamma \\ &= R_o\left(1 + \frac{E\max C_p}{EC_{50} + C_p}\right) + f_p(t) - \gamma \\ &= \beta + \frac{E\max C_p}{EC_{50} + C_p} + f_p(t) \end{aligned} \qquad \text{Eq. (14)}$$

yields the familiar dental pain model of Sheiner, *et. al.*[7] Note that for models in which $R(t) \to 0$ at large $C_p(t)$, $q \to \gamma$. Thus, extension of additive ILVRMs can result in parameter estimates dependent upon γ.

CONCLUSIONS

Extension of linear LV provides a convenient, theoretically justifiable, way to apply indirect response models to OC data – thereby narrowing the field of potential models for incorporating IRM temporal features into analyses.

[‡]Nonmem code supplied by Sheiner and corroborated by Beal via email.

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[‡]Here the safety responses are assumed to be from a single mechanism – not general adverse events.

[‡]The log-transform was applied to both sides in the ILVRM development for this reason