

IMPACT OF DELAYED EFFECT IN CONCENTRATION-QT ANALYSES.

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1. INTRODUCTION

In specific thorough QT studies, in addition to assessment of drug induced mean QT increase, as ruled by ICH-E14 guidance, Exposure-Response analyses are performed to have a comprehensive view of drug effects on QT. Most often, direct linear model linking observed QT change to observed plasma concentrations of experimental drugs are fitted. Depending on study designs or sponsors standards, these analyses have various forms:

- dependant variable: $Y_t = \Delta QT_{C_t}$ is a difference versus baseline which could be time-matched or averaged over several predose values; in some cases $Y_t = \Delta \Delta QT_{C_t}$, computed in removing a placebo term from ΔQT_{C_t} , is considered
- model: $Y_{it_j} = \beta C_i(t_j) + \gamma_{t_j} + u_{ij}$, where i represents the patient and t_j represents the time of evaluation, when time effect is included in the model, or $Y_{it_j} = \beta C_i(t_j) + u_{ij}$ if not.

Then, the magnitude of the drug effect is generally estimated as $\hat{\xi} = \hat{\beta} \times \hat{C}_{max}$ where $\hat{\beta}$ is the slope estimate and $\hat{C}_{max}$ is the observed geometric mean of Cmax.

2. AIM OF WORK

This work has following objectives: assess effect of model misspecification on Concentration - QT analyses, where misspecification is induced by error in covariate

- Mostly due to ignored delayed concentration effect
- But also induced by error in PK concentration measurement

3. DELAYED EFFECTS IN C-QT ANALYSES

Accounting for delayed effects, or more generally non-direct concentration effects, in PKPD analyses is not straightforward:

- even in simplest empirical model: $Y_{it_j} = \beta C_i(t_j - \tau) + \gamma_{t_j} + u_{ij}$
 - non-linear model (in particular for delay parameter, τ)
 - parameter dependant regressor $C_i(t_j - \tau)$ not necessarily observed for every value of τ
- and also for more mechanistic models (biophase, indirect models ...)
- in all cases: rigorous analyses require modelling of both pharmacokinetics and response:

$$\begin{cases} C_i(t_k) = C_{th}(\varphi_i; t_k) e^{\varepsilon_i} \\ Y_{it_j} = f(C_{th}(\varphi_i, s \leq t_j), \theta_i; t_j) + u_{ij} \end{cases}$$
 where C_{th} represents the theoretical PK concentration, which is not observed but is perturbed by a multiplicative error e^{ε_i} , and f is the (possibly non-linear) link function between the theoretical PK concentration and the response.

4. IMPACT OF DELAYED EFFECTS: THEORETICAL RESULTS

- Ignoring delayed effects in C-QT analyses induces a model misspecification issue known as 'error in covariate problem'.
- This phenomenon is known to induce biased parameters estimates: for instance, in the simple regression setting, error in the regressor induces non consistent (downwards biased) estimate of slope.

4.1 Models - Assumptions

- True model assumes linear link between delayed theoretical concentration and response without any time effect (any circadian effect supposed to be removed):

$$Y_{it_j} = b.C_{th,i}(t_j - \tau) + u_{ij}$$

with: b =true slope, τ =true delay between exposure and response, u_{ij} =residual error with, for instance, compound symmetry covariance structure.

- Working analysis model considers observed concentration as predictor, ignores delayed effect but includes time effect as factor.

$$Y_{it_j} = \beta.C_i(t_j) + \gamma_{t_j} + \eta_i + \varepsilon_{ij}$$

with: V the intra-individual conditional (given C) covariance matrix assumed by the model: $V_{k,k} = \sigma_{\eta}^2 + \sigma_{\varepsilon}^2$, $V_{k,l} = \sigma_{\eta}^2$ and $\alpha = (\sigma_{\eta}^2, \sigma_{\varepsilon}^2)$

notations: $Y_i = {}^t(Y_i(t_1), \dots, Y_i(t_K))$, $\Gamma = {}^t(\gamma_{t_1}, \dots, \gamma_{t_K})$, $C_i = {}^t(C_i(t_1), \dots, C_i(t_K))$

4.2 ASYMPTOTIC RESULTS

Assuming number of patients, N , is large, based on asymptotic statistics results, it can be shown that:

- log-likelihood of misspecified model converges to $\mathbb{M}(\beta, \Gamma, \alpha) = \mathbb{E} \left(-\frac{1}{2} \ln |V| - \frac{1}{2} {}^t(Y_i - \beta C_i - \Gamma) V^{-1} (Y_i - \beta C_i - \Gamma) \right)$
- parameter estimates converge to parameter values solving: $\frac{\partial \mathbb{M}}{\partial \beta} = \frac{\partial \mathbb{M}}{\partial \Gamma} = \frac{\partial \mathbb{M}}{\partial \alpha} = 0$

$$\begin{aligned} \hat{\beta} &\xrightarrow{\mathbb{P}} \beta^* = b \frac{\text{Trace}(V^{-1}(\alpha^*) \text{Cov}(C, C_{\tau}))}{\text{Trace}(V^{-1}(\alpha^*) \text{Var}(C))} \\ \hat{\Gamma} &\xrightarrow{\mathbb{P}} \Gamma^* = b \mathbb{E} C_{\tau} - \beta^* \mathbb{E} C \end{aligned}$$

where α^* is the limit value of the estimates $(\hat{\sigma}_{\eta}^2, \hat{\sigma}_{\varepsilon}^2)$ and $C_{\tau} = {}^t(C_{th}(t_1 - \tau), \dots, C_{th}(t_K - \tau))$

It can be concluded from these results:

- Underestimation of slope
 - bias closely linked to correlation between observed and lagged PK concentration
- Time effect reflects discrepancy between false and true estimate of treatment effect at observed timepoints
 - could be used as a metrics for characterizing impact of delayed effect

5. IMPACT OF DELAYED EFFECTS: SIMULATIONS

5.1 Simulation plan

For each scenario (scenarios vary with respect to magnitude of delay)

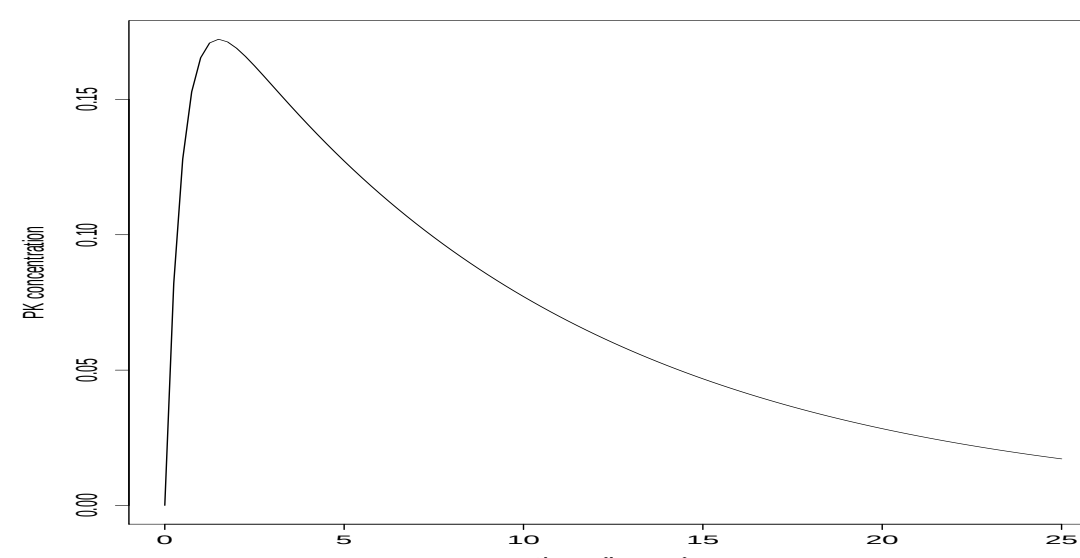
- 2000 studies simulated
- for each study
 - parallel group design
 - 2 doses plus one placebo group
 - 60 patients per group
- Response model (conditional on concentration)
 - slope=1.45
 - conditional covariance structure: compound symmetry with $\sigma_{\eta} = \sigma_{\varepsilon} = 8.0$
- timepoints (in hours): $t = (0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 14)$

The pharmacokinetic data are simulated according to following assumptions:

One compartment, first order absorption model

$$C(t) = \frac{\text{Dose}}{V} \frac{k_a}{k_a - k} \left(e^{-kt} - e^{-k_a t} \right); k = \frac{CL}{V}$$

Parameter	Median value	IIV (CV)
k_a	2.15 h ⁻¹	0.20
CL	0.5 Lh ⁻¹	0.20
V	5 L	0.20



Residual error: $CV = 0.10$

5.2 Results

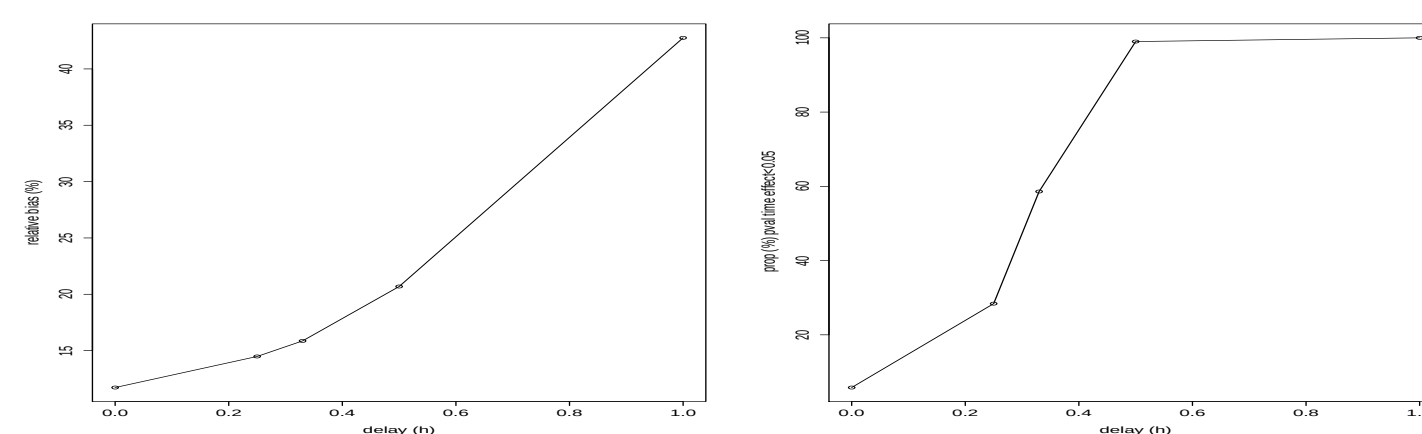
Scenario	mean of β estimate (SE)	MSE	pvalue ^(*) time < 0.05
Delay= 0 h - no covariate error ^(†)	1.45 (0.19)	0.04	5.3 %
Delay= 0 h	1.28 (0.18)	0.06	5.8 %
Delay= 0.25 h	1.24 (0.18)	0.07	28.4 %
Delay= 0.33 h	1.22 (0.18)	0.08	58.6 %
Delay= 0.50 h	1.15 (0.18)	0.12	99 %
Delay= 1 h	0.83 (0.18)	0.41	100 %

SE: standard error

MSE: mean square error

(*) : pvalue of Wald test of time effect in regression model

(†): Scenario assuming that the PK concentration observed is error free (intra-individual variability of C set to 0).



From the simulations, it can be concluded:

- Error in predictor variable induces an underestimation of slope
 - bias increases as lag time increases
 - non negligible bias, $\simeq 12\%$ underestimation, only induced by measurement error (without any lagged effect)
- Magnitude of time effect is influenced by magnitude of lag-time

– assessed here by p-value of Wald test: p-value decreases as lag-time increases

6. ALTERNATIVES WHEN EVIDENCE OF HYSTERESIS

- Gold standard full PKPD modelling (including PK model) can be complex
- Alternative: sensitivity analysis approach

Instead of estimating slope and lag-time simultaneously, try to re-estimate slope in making assumptions on lag-time considered as tuning parameter

 - considering τ known, or assumed
 - asymptotic analysis shows that $\beta_{\tau} = \hat{\beta} \frac{\text{Trace}(V^{-1}(\hat{\alpha}) \text{Var}(C))}{\text{Trace}(V^{-1}(\hat{\alpha}) \text{Cov}(C, \tilde{C}_{\tau}))}$ is unbiased
 - because $\text{Var}(C)$, $\text{Cov}(C, C_{\tau})$ are unknown, in practice:
 - * for each patient, calculate lagged concentration vector using spline interpolation $\rightarrow \tilde{C}_{\tau}$
 - * use empirical estimates of variance and covariance matrices $\widehat{\text{Var}}(C)$, $\widehat{\text{Cov}}(C, \tilde{C}_{\tau})$

lagged time adjusted estimator:

$$\hat{\beta}_{\tau} = \hat{\beta} \frac{\text{Trace}(V^{-1}(\hat{\alpha}) \widehat{\text{Var}}(C))}{\text{Trace}(V^{-1}(\hat{\alpha}) \widehat{\text{Cov}}(C, \tilde{C}_{\tau}))}$$

In practice, would be computed for various values of τ

Simulations: properties of sensivity analyses

Objectives:

Assess the properties of the corrected slope estimate when the true lag-time is considered.

Results

Scenario	adjusted slope estimate $\hat{\beta}_{\tau}$ (SE)	MSE
Delay= 0.25 h	1.30 (0.18)	0.05
Delay= 0.33 h	1.32 (0.19)	0.05
Delay= 0.50 h	1.42 (0.21)	0.05
Delay= 1 h	1.44 (0.31)	0.10

true value of slope=1.45

- Accuracy of asymptotic adjustment roughly satisfying
- MSE largely improved for greater delays

7. CONCLUSION

- Misspecification of model can induce a non-negligible bias in treatment effect estimate
 - Even if only error in PK concentration measurement
 - Also, and especially in case of non-direct concentration effect translating in hysteresis effect
- Various ways to identify hysteresis
 - time-oriented plots of both PK concentration and response, (including hysteresis plots, based on which quantitative criteria can be built, cf Glomb and Ring, JBS, 2012)
 - but also: magnitude of time effect factor in regression (due to high sensitivity to model misspecification and lagged effect in particular)
 - * as a corollary: shows utility of adding time effect to the model, even if all circadian effect are supposed to be removed

• Next steps

- Sensitivity analyses

Assess more natural, alternative method: fit of approximate model: $Y_{it_j} = \beta Z_{\tau}(i, t_j) + \gamma_{t_j} + u_{ij}$ where $Z_{\tau}(i, t_j) = \tilde{C}_i(t_j - \tau)$ with $\tilde{C}_i(\cdot)$ is the spline function interpolating observed PK concentration
- Analyses model
 - * Assess properties of approximate-interpolated model:

$$Y_{it_j} = \beta \tilde{C}_i(t_j - \tau) + \gamma_{t_j} + u_{ij}$$
 (with both β and τ are parameters to estimate)
 - * to be compared to full PKPD approach

8. REFERENCES

White H, *Maximum Likelihood Estimation of misspecified Models*, 1982, Econometrica, Vol. 50, pp 1-25.
Glomb P, Ring A, *Delayed Effects in the Exposure-Response Analysis of Clinical QTc Trials*, 2012, Journal of Biopharmaceutical Statistics, Vol. 22, pp 387-400.