

Dynamic Pharmacodynamics: Modeling and Optimization

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Objectives: Past decades has witnessed the emergence of modeling strategies for both pharmacokinetics (PK) and pharmacodynamics (PD). While the physiological underpinnings of PK models are fairly well understood, it has been more difficult to map knowledge about cellular pharmacology to measured drug effect. Parameterized models such as the sigmoidal Emax, or Hill model provide instantaneous relationships between plasma or biophase concentration with drug effect. When effect depends on history of drug exposure (tolerance, delayed hypersensitivity), dynamic elements must be introduced, as in the indirect response model. In this talk, we describe two pharmacodynamic models that are inspired by cellular signaling and metabolism. The first model describes the development of tolerance to nitroglycerin (glyceryl trinitrate, GTN) seen in cultured cells exposed to GTN at different doses and over different time periods [1]. The second model [2] accounts for variabilities in the apparent Hill coefficient observed between individuals, and also for drug tolerance. This model may correspond to events following binding of drugs to G-protein couple receptors (GPCR's). Finally, we discuss computational and analytical methods for dose optimization in the presence of tolerance [3].

Methods:

GTN modeling: We take as drug effect the concentration of cGMP in cultured LLC-PK1 cells after exposure to extracellular GTN over a prescribed time period at constant concentration [1]. The pharmacodynamic model involves ordinary differential equations (ODE's) corresponding to reaction of GTN with an intracellular factor to produce nitric oxide (NO), GTN-dependent degradation of the intracellular factor, saturable activation of guanylate cyclase (GC) by NO, and conversion of GTP to cGMP by GC. With f denoting activity of the intracellular reactant with GTN and n denoting activity of NO, the ODE's are

$$\frac{df}{dt} = -k_1[GTN]f \quad (1) \quad ; \quad \frac{dn}{dt} = [GTN]f - k_2n \quad (2) \quad ; \quad \frac{d[cGMP]}{dt} = \frac{\alpha_2 n}{\alpha_1 + n} - k_3[cGMP] \quad (3)$$

where the kinetic parameters are determined by fitting against [cGMP] data collected using radioimmunoassay. This model is suitable for early exposure to GTN. Longer term exposure, followed by relief after exposure requires a slightly more elaborate model that includes biosynthesis of a replacable pool of the intracellular reactant with GTN. Here Eq. (1) replaced by

$$\frac{df_1}{dt} = r - (r + k_1[GTN])f_1 \quad (1') \quad ; \quad \frac{df_2}{dt} = -k_1[GTN]f_2 \quad (1'') \quad ; \quad f = f_1 + f_2 \quad (1''')$$

where r is a zero-order biosynthesis rate pertaining to the replacable pool.

GPCR modeling: Drug binding to cellular receptor is assumed to follow a hyperbolic characteristic. A cascade of hyperbolic steps follows, corresponding to activation of adenylyl cyclase (AC), conversion of ATP by cAMP by AC, and phosphorylation of protein kinase A (PKA) by cAMP. PKA in turn activates an effector molecule (E), which is also deactivated by a phosphatase. Tolerance is ascribed to more rapid metabolism of activated E than inactivated E. Effector is assumed to be biosynthesized at a constant rate, and its metabolism is assumed to be first order, with rate constant dependent on its activation state. Assuming that intracellular signaling processes are rapid compared to pharmacokinetics and to metabolism of E, the relevant equations, expressed in dimensionless form, are

$$\frac{d\alpha}{d\tau} = 1 - [1 + (\kappa - 1)f^*]\alpha \quad (4) \quad ; \quad \gamma \left(\frac{\tilde{c}}{1 + \tilde{c}} \right) = \frac{f^* + f^*(1 - f^*)\alpha \tilde{C}_{ET}^0}{1 - f^* + f^*(1 - f^*)\alpha \tilde{C}_{ET}^0} \quad (5)$$

where \tilde{C}_{ET}^0 is the quiescent concentration of E, prior to stimulation by drug, α is the relative availability of E compared to its quiescent value ($\alpha < 1$ indicates tolerance), f^* is the fraction of available E that is activated, κ is the ratio of metabolic rate constants of E in its activated and inactivated states, and γ is the ratio of total activity of E to the Michaelis constants of PKA and the phosphatase, assumed for simplicity to be equal. The latter equation is based on a quasi-steady state between inactive and active E.

Dose optimization: As an example of continuous dose pattern optimization, we consider a variant of a model of nicotine tolerance introduced by Porchet et al. [4], in which tolerance is attributed to buildup up of a metabolite that noncompetitively inhibits saturable binding of drug to an effector. Using dimensionless variables, let c and a represent drug and metabolite concentrations, respectively, and E the drug effect. With drug input $u(t)$, the model is then stated as

$$\frac{dc}{dt} = -c + u \quad (6) ; \quad \frac{da}{dt} = k_a(c - a) \quad (7) ; \quad E = \frac{c}{(1+c)(1+a/a^*)} \quad (8)$$

The goal is to maximize the average fraction of time that E lies within an acceptable range, $[E_1, E_2]$. We imposed periodic boundary conditions on $u(t)$, but permitted its period to be variable. Two optimization algorithms were used, one based on Fourier series and the other based on a presumed piecewise linear solution [4].

Results:

GTN modeling: Eqs. (1)-(3) described an extensive set of data taken after early exposure of cultured cells to various levels of GTN for different time periods. Over longer periods of time, it was necessary to use the two-pool model for GTN reactant kinetics [Eqs. (1')-(1'')] in order to account for incomplete recovery of reactant activity after prolonged exposure followed by relief.

GPCR modeling: Predictions of Eq. (5) were matched to those of the sigmoidal Emax model, giving apparent values of E_{max} , EC_{50} and Hill coefficient, n . When the total concentration (activated and inactivated) of effector significantly exceeds the Michaelis constants of PKA and phosphatase ($\gamma \gg 1$), apparent n becomes strongly dependent on γ , and the other apparent parameters are also affected. Apparent n can greatly exceed unity, even though there is no explicit “cooperativity” built into this model. The apparent Hill coefficient also changes with prolonged exposure to drug and development of tolerance.

Dose optimization: In the presence of tolerance, which ultimately lowers maximal drug effect below a desired threshold, both optimization schemes predicted that the “best” program for periodic drug administration include an initial rapid dosing to place E in the desired range, slower dosing to maintain E in that range, followed by complete shutoff to allow the system to recover when the second step is no longer tenable.

Conclusions: We explored schemes for modeling and dose optimization when PD is dynamic.

References:

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