

Title: Equivalent Constant Concentration Summarizes Pharmacokinetics in HIV and HCV PK/PD Modeling

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Objectives: To define and illustrate the usefulness of Equivalent Constant Concentration in continuous-time PK/PD modeling with concentration linked to Emax viral inhibition, in turn linked to viral dynamics equations.

Methods: Equivalent Constant Concentration (ECC) is defined as the concentration of a drug that produces the same average effect over a time interval (usually a single inter-dose interval) as a time-varying concentration profile [1]. It is constant for a given subject at steady-state drug concentrations. In antiviral modeling, the effect can be taken as viral inhibition $Inh(t)$, which is related to plasma concentration by an Emax equation with E_{max} usually set to 100%. This time-varying viral inhibition enters predator-prey viral dynamics of the form:

$$dU/dt = \lambda - d U - \beta U V, \quad dI/dt = \beta U V - d_I I, \quad dV/dt = p I - c V$$

where U , I , and V are uninfected target (susceptible) cells, infected cells, and virus respectively, and the parameters are birth/activation, death/clearance, and infection rates [2, 3]. Generalizations not considered here include resistant viral strains and in HIV models, latently infected and long-lived infected cells. Typically it is assumed that HCV drugs and protease inhibitors reduce p , while other HIV drugs reduce β , multiplying them by $1-Inh(t)$.

The steady-state viral load obtained by setting these equations to 0 is $(d/\beta) \max(0, R_0-1)$, where $R_0 = \lambda \beta p / (d d_I c)$. R_0 is the reproductive ratio, defined as the average number of secondary infected cells arising from one infected cell placed in an uninfected cell population. Thus the goal of treatment is to drive R_0 below 1 (though this still would not cure HIV due to very slow leakage of virus from sanctuary sites). Even for patients at steady-state concentrations, $Inh(t)$ and hence R_0 vary with time, so the usefulness of ECC rests on whether *average* steady-state viral inhibition gives essentially the same modeled viral loads as $Inh(t)$. Then the minimum dose required for long-term virological success produces the ECC that drives R_0 just below 1.

The equivalence of ECC (or average inhibition) and full PK (or time-varying inhibition) was tested with various illustrative HIV and HCV monotherapy PK/PD models combining standard compartmental PK models, a simple Emax equation, and the viral dynamics above. Extensions to this viral dynamics and also combination therapy modeling were omitted for simplicity. ECC was calculated by the trapezoidal rule like average concentration C_{av} , except averaging inhibitions not concentrations, and converting the result back to a concentration by inverting the Emax function. Note that average inhibition and ECC depend on the IC_{50} of the Emax equation, so ECC is really a summary of more than PK, but the dependence of ECC on IC_{50} is weak (see Results).

For each model, 500 patients were simulated over 48 weeks, and success rates (proportions of patients with viral load less than thresholds such as the limit of detection) were compared over time. Because of the long time horizon, ECC was approximated to be at steady state from the first dose, though it could be calculated for each inter-dose interval until steady state is reached. NONMEM VI Level 1.0 was used to simulate (\$SIMULATION command) with both full PK and ECC. Results were summarized and plotted in Microsoft® Excel 2003. The steady-state viral load of each patient was also approximated as $(d/\beta) \max(0, R_0-1)$ with R_0 multiplied by 1 -average inhibition. The steady-state success rate was found as the fraction of patients for which this was below the limit of detection. The long-term HCV endpoint of sustained virological response was not simulated.

Results: In a typical simulation (Figure 1) the use of ECC gave essentially the same response as full PK, while reducing computation time in NONMEM by 93%. The predicted steady-state success rate was about 10 percentage points lower than the simulated 48-week success rate, indicating that this percentage of patients would fail after 48 weeks even if treatment continues (as for HIV). Patient B in Figure 1a illustrates such a patient, whose viral load becomes undetectable (reaching a nadir of $-1.3 \log_{10}$ IU/mL at 36 weeks) but becomes detectable shortly after 48 weeks. ECC in this example is 79% of C_{av} and depends very weakly on IC_{50} , decreasing 8% when IC_{50} decreases 10-fold and increasing 17% when IC_{50} increases 10-fold. Likewise, while C_{av} is dose-proportional, ECC is 8% below and 17% above dose-proportional when the dose increases and decreases 10-fold respectively.

Conclusions: Average viral inhibition and the corresponding concentration, called ECC, simplify HIV and HCV PK/PD modeling. ECC always falls between C_{min} and C_{av} , due to the concave shape of E_{max} functions and Jensen's inequality, which states that the expectation of a concave function (average inhibition) is less than the function at the expectation (C_{av}). PK-enhancing drugs like ritonavir, which flatten as well as boost concentration profiles of CYP3A4-metabolized drugs, can be seen to improve efficacy both by increasing C_{av} and by increasing the fraction ECC/C_{av} . ECC and average inhibition resolve the dilemma that neither C_{min} nor C_{av} provides a robust PK summary for comparing the efficacy of antivirals, a problem arising with simple efficacy measures such as the inhibitory quotient C_{min}/IC_{50} .

ECC can be used to quickly compare treatment with different dosing frequencies, drug formulations, etc.: treatments providing the same average inhibition should have the same efficacy. Reproductive ratio adjusted for the average inhibition by a regimen allows a quick approximation of the long-term success rate of the regimen. Finally, in long-term simulations the use of average inhibition can reduce computation time greatly without loss of accuracy. It remains to be studied whether the effect on success rates of mediocre adherence to a prescribed regimen (especially relevant to HCV patients, for which the standard of care is hard to tolerate) can be captured adequately by simply derating ECCs, and whether extensions such as multiple drugs and resistant viral strains have much effect on the accuracy of the approximation.

References:

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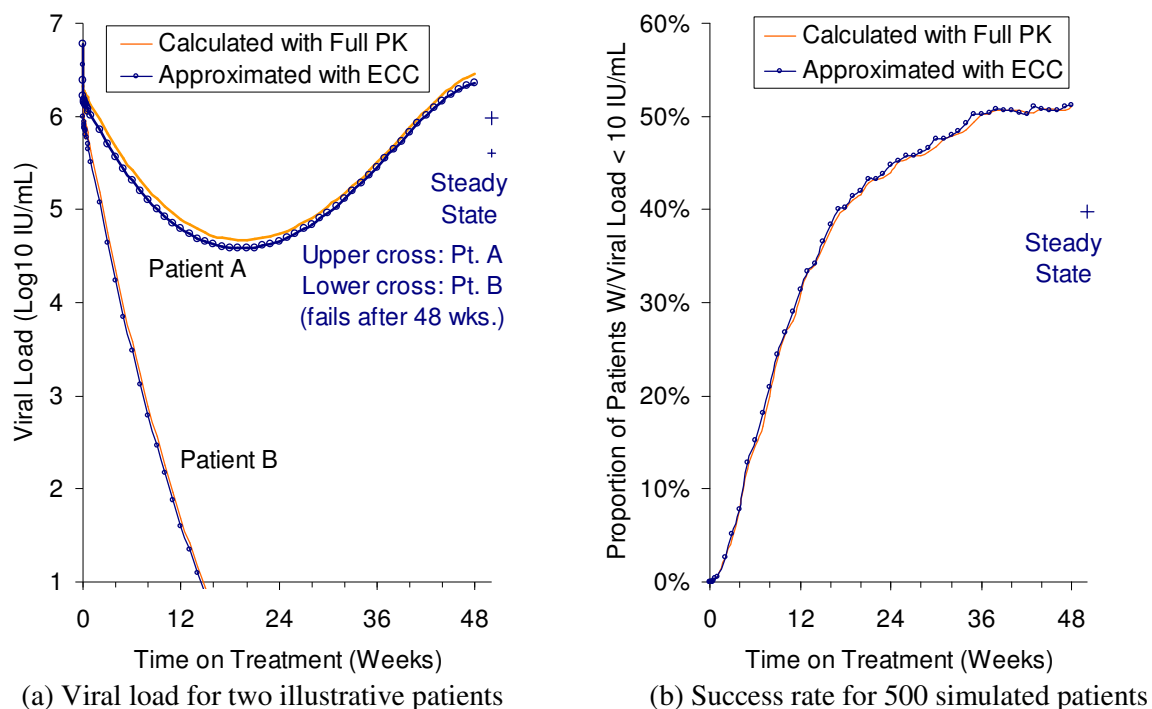


Figure 1. ECC vs. full PK for simulated HCV patients. PK: 100 mg BID, one compartment first-order absorption, $CL=40$ L/h, $V_d=200$ L, $k_A=1/h$. $IC_{50}=0.05488$ mg/L= $ECC/3$ (75% avg. inhibition). Viral dynamics: pre-treatment $R_0=5$ with $\Omega=0.5$ (variance of $\ln(R_0)$), $\lambda=15,000$ cells/mL/day with $\Omega=0.8$, $d=0.00347/day$ (200-day half-life), $\beta=5E-9/(IU/mL)/day$, $p=180$ IU/cell/day, $c=6.16/day$, $d_r=\lambda \beta p/(d R_0 c)$, residual variance $\Sigma=0.15 \log_{10} IU^2/mL^2$.