

Abstract

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

Introduction: 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), which is related to plasma concentration by an Emax equation with Emax usually set to 100%. This time-varying viral inhibition enters predator-prey viral dynamics such as:

$$dU/dt = \lambda - dU - BU \cdot V$$

$$dI/dt = BUV - dI$$

$$dV/dt = pI - cV$$

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]. HCV drugs and protease inhibitors are typically assumed to reduce p , while other HIV drugs reduce B , multiplying them by $1/Inh(t)$.

Methods: The usefulness of ECC rests on whether average steady-state viral inhibition gives essentially the same modeled viral loads as Inh(). This was tested with four illustrative HCV monotherapy PK/PD models combining one-compartment PK, a simple Emax equation, and the viral dynamics above. ECC was calculated by the trapezoidal rule like average concentration Cavg, except averaging inhibitions not concentrations, and converting the result back to a concentration by inverting the Emax function.

For each test model, 500 patients were simulated over 48 weeks, and viral loads and success rates (proportions of patients with viral load less than thresholds) were compared over time.

Results: ECC gave essentially the same response over time as full PK, while reducing simulation time in NONMEM by about 90%. When a resistant viral strain was included in the dynamics, a separate adjusted ECC for that strain improved accuracy.

Conclusions: Average viral inhibition and the corresponding concentration, called ECC, simplify integrated antiviral PK/PD modeling. While the tests here used parameter values appropriate for HCV, comparisons of simulated viral load using ECC vs. full PK with HIV parameters have given similar agreement (see Ref. 1 for use of ECC in HIV modeling). ECC and average inhibition resolve the dilemma that neither Cmin nor Cavg provides a robust PK summary for comparing the efficacy of antivirals, a problem arising with simple efficacy measures such as the inhibitory quotient Cmin/IC50. 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. In long-term simulations the use of average inhibition can reduce computation time an order of magnitude without loss of accuracy.

Introduction

- Equivalent Constant Concentration (ECC) = concentration that produces same average effect over a time interval (usually a single inter-dose interval) as a time-varying concentration profile [1]. See "PK and ECC" figures.
 - This is constant for a given subject at steady-state drug concentrations
- In antiviral modeling, typically effect = viral inhibition $Inh(t) = Conc / (Conc + IC50)$
 - A Hill coefficient can be incorporated easily.

Methods

Time-varying concentrations for each subject in a simulated population were used in a simple Emax model to calculate time-varying viral inhibitions.

One minus these inhibitions multiplied p in predator-prey viral dynamics of the form:

$$dU/dt = \lambda - dU - BU \cdot V$$

$$dI/dt = BUV - dI$$

$$dV/dt = pI - cV$$

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].

Various generalizations of these equations are omitted here for simplicity, such as latently infected and long-lived infected cells in HIV models.

The steady-state viral load obtained by setting these equations to 0 is $(d/B) \max(0, R_e - 1)$, where $R_e = 1 + Bp / (d(c - p))$.

R_e is the reproductive ratio, defined as the average number of secondary infected cells arising from one infected cell placed in an uninfected cell population.

The goal of treatment is to drive R_e 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_e 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 requiring or long-term virological suppression produces the ECC that drives R_e just below 1.

The equivalence of ECC (or average inhibition) and full PK (hence time-varying inhibition) was tested with four illustrative HCV monotherapy PK/PD models combining one-compartment PK, a simple Emax equation, and the viral dynamics above.

ECC was calculated by the trapezoidal rule like average concentration Cavg, 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 IC50 of the Emax equation, so ECC is really a summary of more than PK, but the dependence of ECC on IC50 is weak (see last two ECC's in Results).

For each model, 500 patients were simulated with both ECC and full PK over 48 weeks, and viral loads and proportions of patients with viral load less than a 10 IU/mL 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).

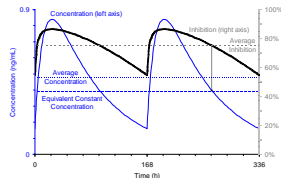
NONMEM VI Level 1.0 was used to simulate (SIMULATION command) with both full PK and ECC. Results were summarized and plotted in Microsoft Excel 2003.

The steady-state viral load of each patient was also approximated as $(d/B) \max(0, R_e - 1)$ with R_e multiplied by 1/average inhibition. The long-term HCV endpoint of sustained virological response was simulated as the proportion of patients with less than 1E5 IU/mL at 48 weeks, corresponding to about 1 virion in the body and thus representing a threshold for cure.

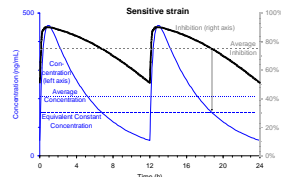
Results

Case PK and ECC 48-Week Simulations: ECC vs. Full PK

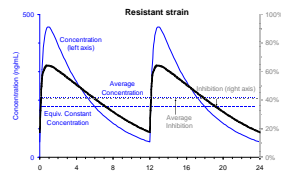
1. Peg-Interferon weekly monotherapy, PK: 1.5 µg/kg x 70 kg weekly, one compartment first-order absorption, $CL=1.5 L/h$, $V_d=101 L$, $t_{1/2}=1.916$ PD: $IC50=0.131$ ng/mL - ECC's (75% avg. inhibition). Pre-treatment $R_e=5$ with $D=0.5$ (variance of $Inh(R_e)$), $N=15,000$ cells/mL/day with $D=0.8$, $d=0.00347$ /day (200-day half-life), $B=5.9$ (10 IU/mL)/day, $p=180$ IU/cell/day, $c=4.16$ /day, $dI=1.8$ p/d (4 c), residual variance $\sigma=0.15$ log₁₀ IU/mL. Note: ECC is found as concentration corresponding to average inhibition (vertical arrow). Even when viral inhibition is averaged over an entire week, the approximation works well.



2. New-mechanism monotherapy, no resistance development. PK: 100 mg BID, one compartment first-order absorption, $CL=40 L/h$, $V_d=200 L$, $k_{el}=3/h$. PD: Same as above except $IC50 = 50.7$ ng/mL - ECC's (75% avg. inhibition) as above. Note: Since the average inhibition was set the same as Case 1, results are very similar. Accuracy is slightly better than Case 1, due to higher dose frequency.



3. New-mechanism monotherapy, 5-fold resistant viral strain present, ECC calculated with sensitive strain only. PK: As above. PD: As above with a resistant as well as sensitive viral strain, and accordingly a resistant-strain-infected cell type (2 additional viral dynamics equations). Resistant strain has 5-fold higher IC50, probability 1E-5 of arising from each sensitive strain replication, and fitness 90% of the sensitive strain. Note: Approximation works well in the first few weeks and becomes slightly pessimistic as resistant virus grows out, because ECC for the resistant strain is 16% higher (17% vs. 152 ng/mL).

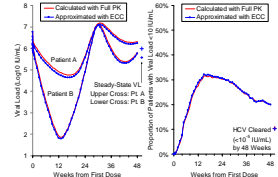
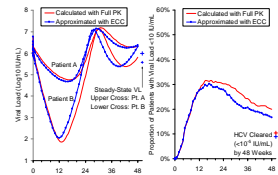
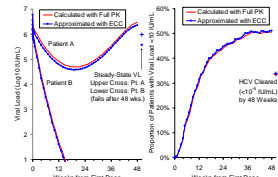
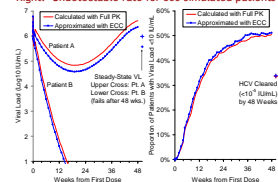


4. New-mechanism monotherapy, 5-fold resistant viral strain present, ECC calculated separately for sensitive and resistant strains. PK: As above. PD: As above with ECC calculated separately with sensitive-strain and resistant-strain IC50s. Note: Calculating a second ECC for resistant virus improves the approximation.



Left: Viral load for two illustrative patients

Right: Undetectable rate for 500 simulated patients



Discussion

Average viral inhibition and the corresponding concentration, called ECC, simplify integrated antiviral PK/PD modeling. While the tests here use parameter values appropriate for HCV, comparisons of simulated viral load using ECC vs. full PK with HIV parameters have given similar agreement (see Ref. 1 for use of ECC in HIV modeling). ECC always falls between Cmin and Cavg, due to the concave shape of Emax functions and Jensen's inequality (the expectation of a concave function, e.g., average inhibition, is less than the function at the expectation, e.g., Cavg). 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 Cavg and by increasing the fraction ECC/Cavg. ECC and average inhibition resolve the dilemma that neither Cmin nor Cavg provides a robust PK summary for comparing the efficacy of antivirals, a problem arising with simple efficacy measures such as the inhibitory quotient Cmin/IC50.

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 an order of magnitude without loss of accuracy. However, it is difficult to incorporate poor or variable adherence to a regimen using ECC; derating ECC to reflect imperfect adherence is a good approximation only at high adherence levels. It remains to be studied whether more complex PK/PD models have much effect on the accuracy of the approximation.

References

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