Original article

A hepatitis C viral kinetic model that allows for time-varying drug effectiveness

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Introduction

Mathematical modelling of early viral kinetics under therapy has been used to understand the effects of therapy on viral load and to estimate key parameters, such as the effectiveness of interferon (IFN) in blocking viral production. Neumann et al. [1] modelled short-term (2-week) hepatitis C virus (HCV) dynamics under high-dose, daily, standard IFN therapy by assuming that the drug effectiveness remains constant after a short pharmacological initial delay. The assumption of constant effectiveness was plausible for the situation that Neumann et al. [1] focused on with IFN administered daily. In clinical practice, however, standard IFN is administered every other day. This, and other changes in the clinical management of HCV, such as weekly administration of pegylated (PEG)-IFN or IFN dose reduction, results in changes in IFN concentration during therapy. In these circumstances the assumption of constant drug effectiveness is violated. We have called models such as those of Neumann et al. [1], Herrmann et al. [2] and Colombo et al. [3], which assume constant drug effectiveness, constant effectiveness (CE) models.

In this study we have introduced a new class of models that allow the drug effectiveness to decrease during therapy. We have called such models decreasing effectiveness (DE) models. The first such model was introduced by Bekkering et al. [4] to analyse data that was obtained when the IFN dose was switched during treatment. In that study, 15 patients received 10 MU of IFN daily for the first 3 days of therapy followed by 3 MU IFN daily for 52 weeks. On average, viral load rebounded by 1.5 log₁₀ copies/ml between days 3 and 4 [4]. Their model described the viral load rebound by assuming that the drug effectiveness declined from a high value to a low value exponentially. Another example of a DE model can be found in the work of Powers et al. [5] and Talal et al. [6], who assumed that the effectiveness of PEG-IFN was related to the drug concentration and that the drug concentration varied in time. In this investigation, both HCV RNA and PEG-IFN-α2b levels were assessed, enabling the development of kinetic models that incorporated time-varying changes in serum IFN concentration. In most viral kinetic studies, however, drug concentration data are not available for each patient. Thus, methods based solely on the measurement of HCV RNA are required for the situation in which drug effectiveness changes...

Background: The standard model of hepatitis C virus (HCV) dynamics under high-dose daily interferon (IFN) therapy assumed that the drug effectiveness remains constant. However, for treatment with pegylated (PEG)-IFN-α2b dosed weekly, drug levels fall substantially and viral load rebounds have been observed toward the end of the weekly dosing interval, implying non-constant drug efficacy.

Methods: In this paper, we developed the decreasing effectiveness (DE) model, a new mathematical model that allows the drug effectiveness to change with time.

Results: The DE model can describe viral load rebounds as well as other viral kinetic patterns observed in clinical practice, such as biphasic viral declines. We applied the DE model to the HCV RNA kinetic data under PEG-IFN-α2b therapy. The average drug effectiveness during the first week of therapy estimated in the DE model agreed with the one estimated from HCV RNA kinetic data plus pharmacokinetic data.

Conclusions: We illustrated the usefulness of the DE model by analysing HCV RNA data from patients who received PEG-IFN-α2b once weekly plus daily ribavirin.
with time. Here we introduce two such DE models and illustrate how one of them can be used to analyse HCV RNA kinetics under PEG-IFN therapy.

Methods

DE model

We studied two different DE models: an exponential model and a linear model in which the drug effectiveness was assumed to decay either exponentially (Figure 1) or linearly. In the following, we explain the DE exponential model only, as the two models are very similar. The description of the DE linear model can be found in Appendix A (see Additional file).

In this DE model, the dynamics of the number of target cells, \( T(t) \), infected cells, \( I(t) \), and of virus, \( V(t) \), are given by

\[
\frac{dT}{dt} = s \cdot \beta V T - dT
\]

\[
\frac{dI}{dt} = \beta V T - \delta I
\]

\[
\frac{dV}{dt} = p(1-\varepsilon(t))I - cV
\]

(Eqn 1)

Cells susceptible to infection, called target cells (\( T \)), are generated at rate \( s \), die at rate \( d \) per cell and are infected with rate constant \( \beta \). Infected cells (\( I \)), die at rate \( \delta \) and produce virus (\( V \)) at rate \( p \) per cell. Virus is cleared at rate \( c \) per virion. Drugs, such as IFN, HCV protease inhibitors and polymerase inhibitors are assumed to reduce virion production with an effectiveness, \( \varepsilon(t) \), that varies between 0 and 1, with \( \varepsilon(t)=1 \) corresponding to a 100% effective drug.

This model differs from the Neumann et al. [1] model only in that the drug effectiveness is an explicit function of time on therapy (\( t \)). To apply this to a situation in which PEG-IFN is administered at time 0, we assume the drug effectiveness (\( \varepsilon(t) \)), for the week after the initiation of therapy is given by

\[
\varepsilon(t) = \begin{cases} 
0 & (0 \leq t < t_0) \\
\varepsilon & (t_0 \leq t < t_m) \\
\varepsilon \exp(-k(t-t_m)) & (t_m \leq t \leq 7) 
\end{cases}
\]

(Eqn 2)

where \( t_m=t_0+t_1 \) and time is measured in days (see Figure 1). By definition, the drug effectiveness is bounded between 0 and 1. Because it takes time for the drug to reach the site of infection and to have an effect in reducing viral production, we assume that the drug effectiveness is zero until time \( t_0 \). For simplicity, we assume that once the drug starts having an effect, its effectiveness attains its maximum (\( \varepsilon \)) very quickly and stays at this maximum until time \( t_m \), after which the effectiveness decays exponentially at rate \( k \). Clearly, a slower ramp-up in effectiveness could be implemented, but this would introduce at least one extra parameter; thus, we have refrained from doing so. The DE model, which allows the drug effectiveness to change with time, is more realistic than the CE model, especially for treatment with PEG-IFN that is administered once weekly. In addition, the DE model has two fewer parameters than the model introduced by Powers et al. [5] and Talal et al. [6] that explicitly considers drug pharmacokinetics. The DE model also has the advantage that it is suitable to estimate parameters based on the viral kinetic data only. Details are discussed later.

Parameter dependence of viral load in the DE model

To describe the changing efficacy (Equation 2), we need four parameters: \( \varepsilon \), \( t_0 \), \( t_1 \) and \( k \). As expected, when maximal effectiveness (\( \varepsilon \)) is larger, the viral load reaches a lower level by time \( t_m \). If the duration that the drug effectiveness remains at its maximum (\( t_1 \)) is larger, then the viral load keeps declining for longer. After time \( t_m=t_0+t_1 \), the viral load rebounds and the decay rate of drug effectiveness (\( k \)) affects the speed of this rebound. If \( k \) is larger, the drug effectiveness declines faster and the viral load also rebounds faster.

Results

Viral load behavior in the DE model

Because of the decline of drug effectiveness, the DE model can describe the viral load rebounds observed toward the end of the weekly dosing interval when PEG-IFN-\( \alpha \)2b is used [6–8]. Also, depending on parameter values, the viral load described by the DE model can have an initial rebound followed by renewed viral decay in the middle of the week (Figure 2A), as seen in some patients treated with PEG-IFN-\( \alpha \)2b plus ribavirin. For example, of the 19 HIV–HCV-coinfected patients analysed below, 6 patients
(1, 7, 10, 16, 66 and 505) showed this mid-week peak of viral load, which occurred on day 5 in patient 1, day 3 in patients 7, 10 and 16 and day 6 in patients 66 and 505.

In the Neumann et al. [1] model with constant target cell levels, the viral load is predicted to fall in a biphasic manner, no matter what the effectiveness value is, as long as \( \delta > 0 \). The higher the effectiveness is, the larger the first phase fall. Thus, why does our model show rebounds when the effectiveness is decreased during therapy? We can provide an intuitive explanation for this partial rebound, by analysing a simpler case where the effectiveness changes in a stepwise manner. As shown in Figure 2B, each time the effectiveness is decreased, the viral load rebounds and then begins to fall. If there were many small decreases, approximating the exponential fall in effectiveness, one would expect to see a more continuous increase in the viral load and ultimately a fall. Figure 2B shows how a decreasing efficacy during the weekly dosing interval can lead to a viral rebound and a subsequent decrease in viral load.

Fitting viral kinetic data using the DE model

We analysed the first week of sequential HCV RNA serum concentration in previously untreated HIV–HCV-coinfected patients who received PEG-IFN-\( \alpha \)-2b once weekly plus weight-based daily ribavirin (see [6] for more details about this study). Parameter values were estimated by performing non-linear least square fitting of the natural logarithm of \( V(t) \) predicted by the DE exponential model (Equations 1 and 2) with \( T \) held constant at its pretreatment steady state value \( T_0 = c \delta (p_c) \), to the natural logarithm of the patient’s viral kinetic data. To simplify the model, we fixed \( t_0 \) at 4, 8 or 12 h as done previously [1,6] and chose the value of \( t_1 \) that corresponded to the best fit, that is, to the smallest sum of squared residuals. The model had six free parameters (\( c, \delta, V_0, \varepsilon, t_1 \) and \( k \)) and one fixed parameter (\( t_0 \)).

There were 24 patients in the Talal et al. [6] study. We did not analyse the data of five patients: patients 3, 12, 31 and 36 were null responders. The viral load rebound during the first week of therapy was <1 log_{10} copies/ml and patient 26 had too few viral load measurements during the first week to use our method. Therefore, we analysed data from 19 patients. The fits obtained are shown in Figure 3A and the estimated parameter values are shown in Table 1. Note that the DE model produces a fit that agrees well with the data but, in some patients, tends to have a plateau rather than a monotonic increase in HCV RNA towards the end of the dosing interval. When we previously analysed this same data with the pharmacokinetic/pharmacodynamic (PK/PD) model of Talal et al. [6], the fits in some patients showed more of a rebound, that is, a more monotonic increase in viral load towards the end of the dosing interval. Furthermore, the DE model tended to produce higher estimates of \( \delta \) than the model of Talal et al. [6] (Table 1).

Accuracy of the average effectiveness

Powers et al. [5] and Talal et al. [6] analysed sequential measurements of both HCV RNA and PEG-IFN concentration using both PK and PD modelling. By contrast, we estimated parameters using only the sequential HCV RNA data. Intuitively, we would expect that the PK/PD method would provide more accurate results because this type of analysis is based on more information. Therefore, it is interesting that the estimated values for the average drug effectiveness given by the DE model and by the PK/PD method for the same set of patients [6] were in close agreement (Figure 4). Using linear regression to analyse the relationship between the two

HCV kinetic model with time-varying drug efficacy
Figure 3. Viral load data fits

(A) Best fits for the hepatitis C Virus (HCV) RNA data of HIV–HCV-coinfected patients receiving pegylated interferon-α2b once weekly plus daily ribavirin with the exponential decay decreasing effectiveness (DE) model (parameters given in Table 1). (B & C) Best fits of the exponential decay DE model (solid line) and linear decay DE model (dashed line) to HCV RNA declines of two patients, (B) one showing a viral rebound and (C) one showing a more typical biphasic decline. The delay ($t_0$) in both was fixed at 4 h.

(A) Best fits for the hepatitis C Virus (HCV) RNA data of HIV–HCV-coinfected patients receiving pegylated interferon-α2b once weekly plus daily ribavirin with the exponential decay decreasing effectiveness (DE) model (parameters given in Table 1). (B & C) Best fits of the exponential decay DE model (solid line) and linear decay DE model (dashed line) to HCV RNA declines of two patients, (B) one showing a viral rebound and (C) one showing a more typical biphasic decline. The delay ($t_0$) in both was fixed at 4 h.
sets of results, we obtained \( \varepsilon_{aD} = 0.98 \varepsilon_{aT} - 0.057 \), where \( \varepsilon_{aD} \) and \( \varepsilon_{aT} \) are the average effectiveness estimated by the DE model and by the method of Talal et al. [6], respectively. The slope was not different from one (\( P = 0.88 \)) and the intercept was not different from zero (\( P = 0.55 \)), indicating that the DE model performs well in estimating the average efficacy. The Mann–Whitney U test also indicates that the average effectiveness estimated by the two methods are not significantly different (\( P = 0.14 \)).

Predicting the patient’s virological response from kinetic parameters

In the CE model, the steepness of the second phase decline (which is approximately equal to \( \varepsilon \delta \)) should affect viral negativity at the end of therapy. Thus, it is of interest to compare the estimated \( \varepsilon \delta \) in patients who are sustained virological responders (SVR) with those that are not (non-SVR). When \( \varepsilon \) is close to 1, as was found for high-dose, daily IFN therapy, it suffices to compare values of \( \delta \), as was done in Neumann et al. [1]. However, in this study with PEG-IFN-\( \alpha \)2b, the average drug effectiveness during the first week of therapy was 0.64 [6]. Of the 19 patients studied, 3 patients (5, 17 and 32) were not followed long-term because of adverse effects of therapy. Thus, we focused on the rest of the patients (SVR \( n = 6 \): patients 1, 7, 10, 16, 502 and 503; non-SVR \( n = 10 \): patients 2, 4, 6, 9, 19, 34, 53, 64, 66 and 505). As shown in Figure 4B, the steepness of the second phase slope (\( \varepsilon \delta \), where \( \varepsilon \) is the average drug effectiveness in the first week of therapy) was significantly different between SVR and non-SVR patients, both when Talal et al.’s [6] model (\( P = 0.01 \)) and the DE model (\( P = 0.03 \)) were used to analyse the data (two-sample Student’s \( t \)-test with Welch’s correction). Plotting a receiver operating characteristic (ROC) curve, we found that the best cutoff value of \( \varepsilon \delta \) estimated by the DE model to discriminate between SVR and non-SVR was 0.23. The true positive rate and the false positive rate were 0.90 and 0.23, respectively. The area under the ROC curve was 0.82. When using the CE model, the infected cell loss rate was estimated as zero for 13 of 16 patients (data not shown) because this model cannot describe a viral load rebound [9,10], and therefore could not discriminate between SVR and non-SVR.

**Discussion**

The constant efficacy model described by Neumann et al. [1], and widely used to analyse HCV dynamics under antiviral therapy, describes the biphasic decline of viral load. The model has generally been used assuming that the target cell level is constant during the period

<table>
<thead>
<tr>
<th>Patient</th>
<th>( c ), Day(^{-1} )</th>
<th>( \delta ), Day(^{-1} )</th>
<th>( V_0 \times 10^6 ), IU/ml</th>
<th>( \varepsilon_{aD} )</th>
<th>( \varepsilon_{aT} )</th>
<th>( \tau_0 ), h</th>
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<td>0.06</td>
<td>4.81</td>
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<tr>
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<td>15.67</td>
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<tr>
<td>Minimum</td>
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<td>0.01</td>
<td>0.02</td>
<td>0.18</td>
<td>0.27</td>
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<td>0.24</td>
<td>4.33</td>
<td>0.57</td>
<td>0.64</td>
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</table>

Subscripts \( D \) and \( T \) indicate values estimated by the decreasing effectiveness (DE) model (used in this study) and the pharmacokinetic/pharmacodynamic model used by Talal et al. [6], respectively. \( c \), Clearance rate of free virus; \( \tau_0 \), the delay of drug to be effective on the site of infection (this parameter was fixed in the fits); \( V_0 \), initial concentration of hepatitis C virus RNA in serum; \( \delta \), loss rate of infected cell; \( \varepsilon \), average drug effectiveness. Parameters \( c \) and \( \tau_0 \) were estimated by the DE model.
that viral kinetic analyses are performed, and this leads to a simple analytical solution of the model for $V(t)$, the viral load decline during therapy [1]. This solution shows that virus declines exponentially or bi-exponentially with time during therapy, possibly reaching a flat second phase. However, this solution is not compatible with the viral load rebound that is often observed under PEG-IFN-$\alpha_2b$ therapy. In addition, we found that the use of this solution can generate incorrect parameter estimates under PEG-IFN-$\alpha_2b$ therapy [9,10].

Here we developed a new model, the DE model, that allows for viral rebound as drug effectiveness decreases.

To describe the decrease in effectiveness with time on therapy, two more parameters than the CE model of Neumann et al. [1] are required. However, as we have shown with frequent viral load measurements, enough data are available to fit the DE model. We previously suggested simultaneously measuring the drug concentration and the HCV RNA level, and then using a pharmacodynamic model to relate the drug concentration to its effectiveness [5,6]. This method can also describe viral load rebounds, but requires that drug concentration data be available. In most clinical viral kinetic studies, frequent measurements of drug concentration

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**Figure 4.** Comparing the results of the DE and the PK/PD models

(A) The average effectiveness estimated using the Talal et al. [6] pharmacokinetic/pharmacodynamic (PK/PD) model ($e_{aT}$) and by using the decreasing effectiveness (DE) model ($e_{aD}$) for each of the 19 patients. Formulas for computing the average effectiveness are shown in Appendix B (see Additional file). The linear regression line is given by $e_{aD} = 0.98 e_{aT} - 0.057$. (B) The estimated value of $e_{aD}$, where $e$ is the average drug effectiveness during the first week of therapy estimated either by the method of Talal et al. [6] ($e_{aT}$) or by the DE model ($e_{aD}$) for sustained virological responders (SVR) and non-SVR patients. The $P$-value was calculated by a two-sample Student’s t-test with Welch’s correction for unequal variance.
are not made. Thus, the advantage of the DE model is that it can be used on data sets where only viral load data are available. Furthermore, we have shown that our model can fit patient data (Figure 3A) and produce estimates of drug efficacy that are not statistically different from those obtained with a PK/PD model and knowledge of drug concentration at each time point (Figure 4). In part, this is possible because our previous work analysing PEG-IFN-α2b PK data [5,6] showed that the drug concentration increases very rapidly in the serum (commensurate with our assumption of an instantaneous jump in efficacy from zero to ε in the DE model); also, after a short period (corresponding to t; in the DE model), the drug concentration shows an approximately exponential decrease (mimicked in the DE model). Finally, we showed, albeit on a small number of patients, that the results from the DE model fits can be used to predict SVR, much in the same way as the full PK/PD model. This prediction is not possible with the simpler CE model.

One can consider other forms of the DE model, such as one with a linear decrease in effectiveness. The DE models, either with the exponential decrease or with the linear decrease, have the same number of parameters; we chose to use the former because it mimics the exponential fall in drug concentration. However, because effectiveness is related to drug concentration by a PD model, such as the Emax model [11], it is possible for the drug concentration fall not to translate into an effectiveness fall that is as rapid as one that is exponential. In such cases the linear DE model might be appropriate. In Figures 3B and 3C, we show in two typical patients from [6], one with a viral load rebound and one with a biphasic viral load decline, that the linear DE model gives a fit similar to that of the exponential DE model.

In this paper, we analysed the viral kinetic data of patients who received PEG-IFN-α2b. Whether the DE model should be used to analyse viral kinetic data obtained in patients treated with PEG-IFN-α2a needs to be explored. Previous studies have used the CE model for this PEG-IFN formulation [12–14]. The long half-life of PEG-IFN-α2a (mean 80 h, range 50–140) [15] compared with that of PEG-IFN-α2b (mean 40 h, range 22–60) [16] leads to a monotonic decline of viral load in many patients and would support the use of the CE model. However, some patients treated with PEG-IFN-α2a show viral rebounds between doses [2,12]. For these patients the DE model would be appropriate and we recommend that it be studied in the analysis of their viral kinetic data. For patients in clinical trials treated with PEG-IFN plus an HCV protease or polymerase inhibitor we expect that the CE model would be sufficient if the protease or polymerase inhibitors are appropriately dosed such that their efficacy remains high and HCV RNA declines are monotonic. The CE model has fewer parameters than the DE model and, unless a rebound is seen, the additional parameters in the DE model would be difficult to estimate.

In summary, we have developed a new HCV kinetic model that takes into account the fact that drug efficacy could decrease between dosing intervals. We have shown that this DE model can be used to fit HCV RNA data under once weekly PEG-IFN therapy and allows a robust estimate of the efficacy of this drug.

Acknowledgements

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Disclosure statement

ASP is a consultant for Schering–Plough Research Institute. AHT is on the Speaker’s Bureau and has received research funding from Schering–Plough. All other authors declare no competing interests.

Additional file

The additional file ‘Appendix A and Appendix B’ can be accessed via the Volume 13 Issue 7 contents page for Antiviral Therapy, which can be found at www.intmedpress.com (by clicking on ‘Antiviral Therapy’ then ‘Journal PDFs’).

References


