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Estimating Health Outcomes of Antiviral Use in Influenza Outbreaks by Linking PK/PD and Epidemiology via a Transmission Dynamic Model: A Novel Approach

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BACKGROUND AND OBJECTIVES

- To date, even the most sophisticated mathematical modeling approaches for influenza pandemic planning do not consider basic features of antiviral pharmacology. Indeed the best examples typically consider drug effect as either "on" or "off" in terms of viral transmission, with little consideration of variability in PK and drug response (PD).
- Accordingly, we sought to incorporate antiviral pharmacology into influenza epidemiology models in a semi-mechanistic manner, thus gaining a greater understanding of the potential impact that PK and PD variability has on disease resolution. This approach may provide an improved understanding of the potential impact which differing antiviral strategies (such as dose and deployment) may have on the population burden of influenza infection.

METHODS

Overview

- A single, semi-mechanistic framework was established to assess quantitatively the impact of oseltamivir pharmacology and treatment approaches on the burden of influenza infection in a hypothetical population of 100,000 individuals across a 1-year influenza season.
- The quantitative method incorporated PK/PD variability, and connected three discrete quantitative modules from across the pharmacology and epidemiology disciplines: a population PK model for oseltamivir; a PK/PD evaluation of oseltamivir carboxylate (OC, active metabolite) on viral shedding; and a SEIR (sensitive, exposed, infected, recovered) compartmental epidemiology model.

Oseltamivir PK/PD

- A previously published oseltamivir population pharmacokinetic model was used to simulate oseltamivir pharmacokinetics in 5000 adult patients receiving 75 mg and 150 mg twice daily (Kamal et al. AAC 2013). The proportion of patients with oseltamivir AUCs above the previously identified PK/PD viral shedding threshold (14,180 ng.h/ml) (Rayner et al. AAC 2013) for 75 mg twice daily and 150 mg twice daily regimens were calculated (see **Figure 1**).
- Monte Carlo simulations were conducted for each dose regimen, sampling from the oseltamivir population AUC distributions to construct a density distribution of the populational fraction (F) achieving target attainment. For each patient at a given dose, an individual duration of viral shedding (Tshed, γ) value was assigned based on AUC target attainment. An exponential Tshed distribution with a mean (SD) γhi of 1.9 (0.51) days; for those less than the PK/PD target a mean (SD) γlo of 3 (0.58) days; and for patients not receiving drug a mean (SD) γ0 of 6 (2.5) days was use (Rayner et al. AAC 2013).

METHODS

Epidemiological Model

- We used a stochastic susceptible-exposed-infected-recovered (SEIR) epidemiologic model, adapted to incorporate the impact of antiviral therapy. (see **Figure 2**)
- Differential equations describing the model are:

$$\frac{dS}{dt} = -(\frac{\beta}{N})SI \quad (1)$$

$$\frac{dE}{dt} = (\frac{\beta}{N})SI - E \quad (2)$$

$$\frac{dI}{dt} = E\kappa - F_0\gamma_0 I - F_{AUChi} \times \gamma_{hi} I - F_{AUClo} \times \gamma_{lo} I \quad (3)$$

$$\frac{dR}{dt} = F_0\gamma I + F_{AUChi} \times \gamma_{hi} I + F_{AUClo} \times \gamma_{lo} \quad (4)$$

- Where S = number in the population susceptible to influenza, E = number in latent stage of infection, I = infected, and R = recovered from infection and are immune to re-infection, β governs infectivity, and is a composite of both frequency of individual interactions (population density and social behaviors), and the probability that an interaction will result in a successful influenza infection in a susceptible individual (infectiousness). K = transit time from E to I. F0, FAUClo, and FAUChi represents the fraction of the simulated population not receiving therapy, or with an oseltamivir AUC less than or greater than 14,180 ng.h/mL, respectively.

Monte Carlo Simulations

- PK and PK/PD distributions described above were inputs for the SEIR model simulation scenarios. The scenarios evaluated included the % of the infected population treated with 150 mg or 75 mg twice daily oseltamivir (0, 25%, 50%, and 80%) and two possible attack rates: a modest attack rate of 370/1000 infected (~Ro of 1.9), and a higher attack rate of 670/1000 (~Ro of 2.7) (Collizza et al, Plos Med 2007). Parameters of β were adjusted to achieve the requisite attack rate as outlined in Table 1.
- For each scenario, 1000 Monte Carlo simulations (flu seasons) were completed to provide the following outputs: (i) the number of epidemics where more than 5000 infected cases in the 100,000 population occurred and (ii) the median attack rate (infected cases per 1000 of available population). All simulations were conducted in Berkley Madonna. Parameter values in **Table 1.**

RESULTS

- The SEIR model had the capacity to provide results in general agreement with prior data as shown in **Figure 3a.** Nevertheless, following 1000 simulations (**Figure 3b**) there is extensive variability between simulated flu seasons and the likelihood of an epidemic occurring, supporting using the median behavior of the system and the percentage of simulations where a threshold (5% infected population) was achieved as endpoints.
- In **Figure 4**, when no treatment was provided, 623 of the 1000 simulated seasons resulted >5% of the population being infected with influenza. The overall average number of infected individuals (attack rate) was 370 per 1000. For a virus with higher transmissibility (β = 0.41), 921 of 1000 seasons had >5% of a population infected, and an overall average attack rate of 675 cases per 1000.

RESULTS

Table 1. Baseline parameters for incorporation into Monte Carlo simulations

Descriptor	Value
Population size (N)	100,000 cases
Latency period (1/κ)	1 day [13, 14]
F_{AUChi} 150mg BID, P(AUC>14,180 ng.h/ml)	0.795 +/- 0.095
F_{AUChi} 75mg BID, P(AUC>14,180 ng.h/ml)	0.326 +/- 0.048
γ_0 (No treatment)	6 +/- 2.5 day^{-1}
γ_{lo} (AUC 0 to 14,180 ng.h/ml))	3 *Exp(normal(0,0.58) day^{-1}
γ_{hi} (AUC>14,180 ng.h/ml)	1.9 *Exp(normal(0,0.51)) day^{-1}
β, Moderate transmission rate	0.21
β, High transmission rate	0.41

Figure 1. Histogram of OC $AUC_{0\text{-}24}$ distributions for adults receiving either 75mg BID and 150mg BID. Red and blue indicates subjects with OC AUC < and >14,180ng.h/mL PK/PD threshold respectively.

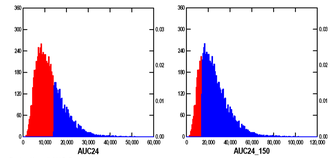


Figure 2. Schematic of SEIR Influenza Epidemiology Model

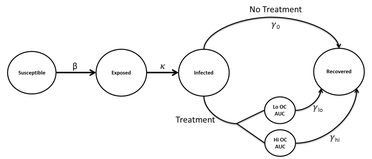


Figure 3. a) Fit of the SEIR Model to 2007-2008 Influenza Data From the Midwestern United States. The grey dotted line represents model fitted function (Beta 0.73, gamma 4.1 d); solid black line represents actual data. b) Example Monte Carlo simulation output for a given scenario. In this case it reflects 1000 Influenza seasons simulated for an influenza virus with β = 0.21 where no subjects received oseltamivir treatment.

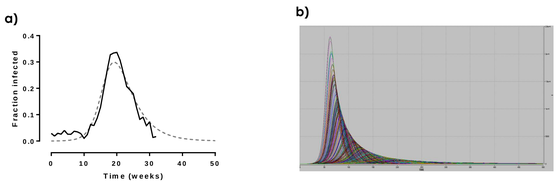
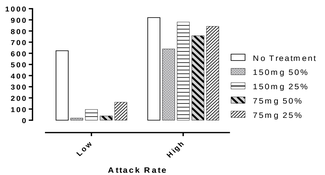


Figure 4. Frequency of simulations with population infection rates exceeding 5000/100,000 for low and high transmissibility scenarios.



- Antiviral treatment under all conditions reduced the number of simulated seasons where an influenza infection rate was >5%; The likelihood of an influenza season being extinguished was higher with low transmissibility scenarios; The likelihood of >5% of the population being infected was reduced with both increasing treatment rates and with a 150 mg dose of oseltamivir.
- The mean number of infected individuals for the two attack rate scenarios is summarized in **Table 2**.
- As expected, the results are sensitive to the magnitude and variability distributions used for the impact of oseltamivir on Tshed. As these results are based on an influenza challenge model, the translation to a seasonal or pandemic situation should be considered.

Table 2. Number of infected individuals of 100,000 by % treated and oseltamivir dose regimen for the modest and a higher attack rate virus scenarios

% Treated	No Treatment	75mg bid	150mg bid
Moderate transmissibility			
25%	37,068	5,133	3,255
50%	--	1,060	481
80%	--	467	85
High transmissibility			
25%	67,512	59,329	53,032
50%	--	41,331	31,700
80%	--	20,941	12,881

CONCLUSIONS

- These results demonstrate that antiviral pharmacology (PK/PD) should be considered as an important component to inform influenza epidemiology models, as oseltamivir dose and variability in PK/PD influenced influenza infection rates.
- The linkage of PK/PD to influenza epidemiology also suggests that antiviral PK/PD can be used to optimise treatment not only at an individual patient level, but may also have indirect benefits reducing societal flu burden. Such approaches may be useful to inform containment strategies, and may offer utility for evaluating the potential impact other antivirals.
- This work has been extended to health economics in Abstract 1715, linking Pharmacology to the Payer