Citation: Clin Transl Sci (2021) 14, 5–7; doi:10.1111/cts.12936

COMMENTARY

Dose Selection in a Pandemic: A Framework Informed by the FDA Animal Rule

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Effective treatment approaches in a pandemic, such as coronavirus disease 2019 (COVID-19), hinge on expeditious identification of sound dosing strategies. Informed by experience with the US Food and Drug Administration (FDA) Animal Rule, this commentary illustrates a framework for leveraging and integrating clinical pharmacology information for dose selection to treat novel infections in a public health emergency setting.

Fighting a novel pathogen like severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, involves coordinated response planning for efficient and rapid detection, diagnosis, prevention, and treatment.[1] An efficient approach to identify treatments for a novel pathogen is to repurpose a drug that has been approved or is under development for other indications. Effective treatment approaches in a pandemic hinge on expeditious identification of sound dosing strategies of drugs and biologics targeting the infecting pathogen. In the early stage of a pandemic outbreak, little is known about the novel pathogen and the disease it causes. In this setting of great uncertainty, leveraging known clinical pharmacology information for dose selection is vital for effective treatment of infection.

HUMAN DOSE SELECTION UNDER THE ANIMAL RULE: A FRAMEWORK FOR PANDEMICS

The dose selection framework outlined in the FDA Animal Rule regulation provides an approach for dose determination in settings of urgent need with limited information. The genesis of the Animal Rule development pathway followed the 2001 anthrax attacks on the US government and journalism outlets and underscored the importance of bio-preparedness and response.[2] The FDA Guidance for Industry entitled *Product Development Under the Animal Rule* outlines essential components and considerations for developers of medical countermeasures for indications where adequate and well-controlled efficacy studies in humans cannot be ethically conducted or are not feasible, as is the case with weaponized pathogens.[3] Emerging infections and pandemic crises present similar developmental challenges. Although clinical efficacy studies are feasible, efficacious and safe treatments are urgently needed at a time before clinical experience and knowledge are available. Thus, dose selection principles similar to those under the FDA Animal Rule development paradigm can inform the approach to determining effective and safe dosing regimens for pandemic infections and offers practical examples to aid development and response during a pandemic emergency.

Under the Animal Rule, selection of an effective dose requires integration of a drug's mechanism of action and antimicrobial activity, pharmacokinetic (PK) and pharmacodynamic (PD) knowledge gained from preclinical experience (both *in vitro* and *in vivo*), and any known PK and PD characteristics of the drug or biologic in humans.[3] Similarly, this information exists in various forms for new drugs in development or drugs marketed for indications other than the pandemic-related need. The information can be assimilated and repurposed for determining dose regimens to treat infections caused by novel pandemic agents.

Mechanism of action and antimicrobial activity

In the setting of a pandemic, selection of an effective dose for prophylaxis and/or treatment of an infection requires a reasonable understanding of the mechanism of action of the drug and data supporting its antibacterial or antiviral activity, as appropriate. An understanding of the mechanism of action provides a foundational hypothesis for a drug's candidacy and may aid in the identification of specific safety or efficacy issues, interpretation of findings in future studies, and identification of additional studies that should be performed.[3]

In vitro assessment of a drug's antimicrobial activity against the pathogen should follow delineation of a mechanistic basis. For antibacterials, this includes determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration, any persistent postantibiotic effects, as well as patterns of killing activity (concentration-dependent or time-dependent killing).[4] For antivirals, studies should be performed to determine specific antiviral activity using an appropriate quantitative assay to measure virus replication in the presence of increasing concentrations of the drug compared with replication in the absence of the drug.[5] The concentration at which virus replication is inhibited by 50 percent (e.g., half-maximal effective concentration (EC_{50}) for cell-based assays and half-maximal inhibitory concentration (IC_{50}) for biochemical or subcellular assays) should be determined. If applicable, activity should be assessed via assay methodology relevant to the site of

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Received: October 7, 2020; accepted: November 15, 2020. doi:10.1111/cts.12936

infection (e.g., determining antiviral activity in a lung epithelial assay for a pathogen causing pneumonia).[5]

PK and PD knowledge informing dose determination

Knowledge of PK characteristics for drugs considered for prophylaxis and/or treatment in a pandemic is essential for determination of dosing regimens likely to be effective and safe. The absorption, distribution, metabolism, and excretion characteristics of the drug in both the preclinical setting and in humans should be well-characterized. Potential interactions with medical products likely to be used concomitantly in the clinical scenario should be evaluated via *in vitro* and *in vivo* methods, if feasible. Using knowledge of absorption, distribution, metabolism, and excretion properties, the effects of the infection and patient characteristics on the disposition of the drug should be predicted, if not previously obtained from clinical experience with other infections. Model-informed methods, such as physiologically-based PK modeling can aid in understanding PK behavior and predicting concentrations at the site of infection (e.g., tissue or intracellular concentrations).[6]

Antimicrobial PD describes the relationship between drug exposure and antimicrobial effect.[4] Relating MIC or EC_{50} values, for bacteria and viruses, respectively, to free drug exposure parameters (e.g., area under the plasma concentration-time curve (AUC), maximum plasma concentration (C_{max}), minimum or trough plasma concentration (C_{min} or C_{trough}, respectively), etc.) informs selection of doses that are predicted to be effective. Calculation of PK/PD parameters, such as C_{max}/MIC, AUC/MIC, and time above MIC (T > MIC) for antibacterials and the C_{min}/serum-adjusted EC_{50} value (inhibitory quotient) for antivirals assimilates *in vitro* data and *in vivo* exposure, providing exposure targets for dosing regimen design. PK/PD data from *in vitro* dynamic models and preclinical (i.e., animal models of infection) and clinical experience with other infections provide useful outcome data and biomarkers to inform target concentrations or exposures predicted to be efficacious.

Integration of clinical pharmacology data for determining dosing regimens in a pandemic setting

Under the Animal Rule, the totality of this clinical pharmacology information forms the foundation of human dose selection and enables translation of efficacy to humans where efficacy data are nonexistent. Given the lack of clinical experience early in outbreaks of novel infections, such as COVID-19, a similar approach applies (**Figure 1**). Mechanism of action and antimicrobial activity determines a drug's potential as a candidate for treatment. These characteristics are integrated with PK and PK/PD knowledge, as well as clinical experience with the drug for other infections, particularly those with similar sites of infection, to inform dosing regimens yielding exposure predicted to be efficacious and safe in the emergency setting.

The repurposing and approval of levofloxacin for treatment of pneumonic plague under the Animal Rule serves as a helpful example of this integration. Levofloxacin is a fluoroquinolone antibiotic marketed to treat several types of

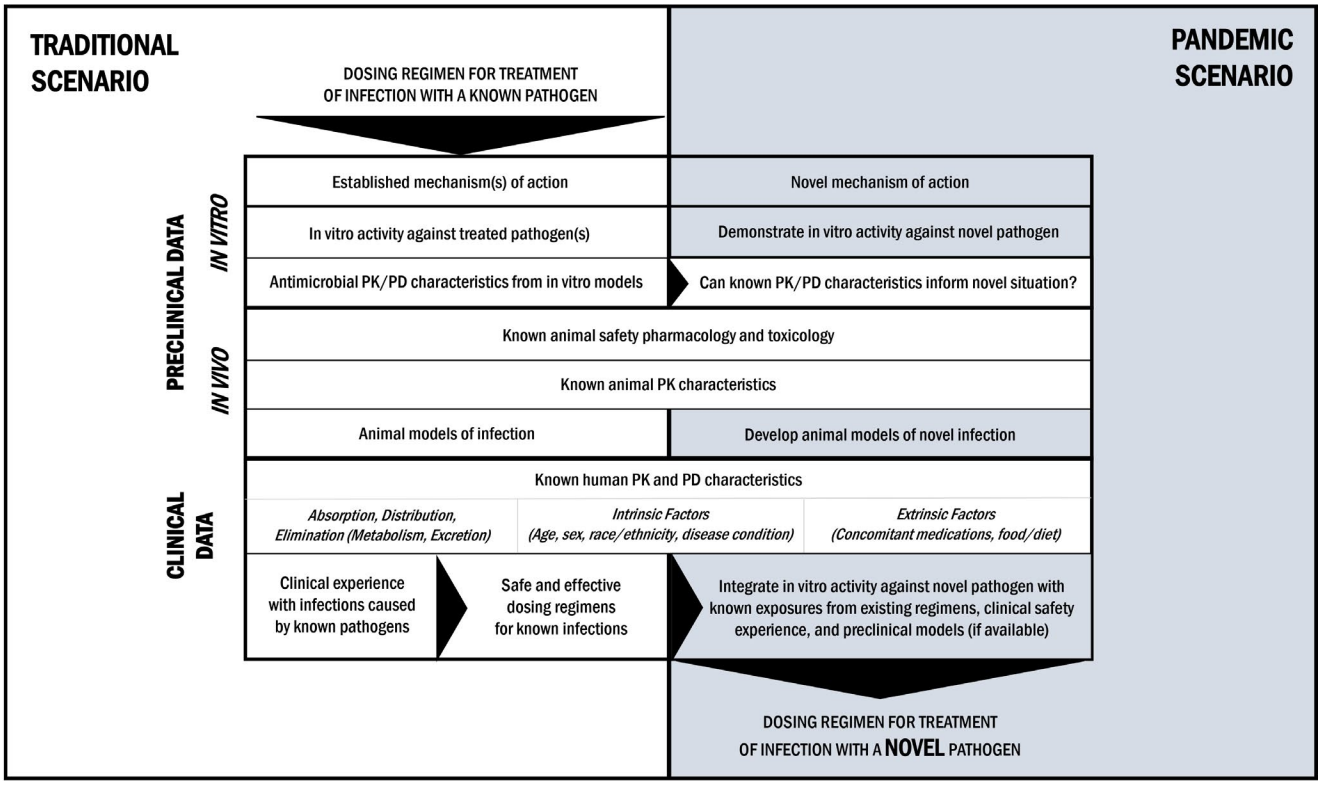

Figure 1 Framework for integration of clinical pharmacology data for determining dosing regimens in a pandemic setting. PD, pharmacodynamic; PK, pharmacokinetic.

infections, and its PK and PD properties are well-characterized. Low MICs and minimum bactericidal concentrations of levofloxacin against *Yersinia pestis* identified it as a potential candidate for the treatment of plague.[7,8] PK/PD data from an *in vitro* hollow-fiber model simulating free drug exposure with approved dosing regimens demonstrated efficacy against *Y. pestis*.[8] The efficacy of levofloxacin to plague was demonstrated in an African green monkey model of inhalational plague with lower to similar plasma exposure of levofloxacin to human subjects.[7] Given the totality of information for levofloxacin (PK/PD data, safety and efficacy data in treatment of lower respiratory tract infections, tissue distribution data, and animal model of infection), levofloxacin was approved for treatment of pneumonic and septicemic plague at previously approved dosing regimens.[7]

An integrative approach similar to that used for the Animal Rule can be applied to selection of dosage regimens for treatment of COVID-19. One example is the investigational drug remdesivir. Remdesivir, a prodrug of the monophosphate nucleoside analog GS-441524, was originally developed for treatment of Ebola virus infection, and the PK and safety of remdesivir and GS-441524 have been evaluated in healthy subjects. Low *in vitro* IC_{50} and IC_{90} values for remdesivir against SARS-CoV-2 made it a potential candidate for COVID-19 treatment.[9] Moreover, remdesivir showed promise in the rhesus macaque model of SARS-CoV-2 infection by reducing viral replication in lungs and demonstrating less severe pneumonia with predicted drug concentrations similar to healthy human subjects.[9,10] Collectively, these types of *in vitro* antiviral activity data, preclinical efficacy findings in animal models, and a PK integration to human exposure from prior clinical experience has the potential to support dosing regimens to be evaluated for COVID-19 therapies.

Regardless of the approach used to integrate PK and PD information for selection of a potentially effective human dose in a pandemic setting, the risks and benefits of the drug must be considered. A less than favorable safety profile may limit the use of higher doses that might be necessary based on a target exposure derived from preclinical data, ruling out a candidate's utility. Additionally, as the emergency event progresses and preclinical and clinical studies are underway, a growing understanding of exposure-response relationships with relevant efficacy and safety end points, outcomes of interest, and biomarkers can inform the evaluation and refinement of dosing regimens. Outcome data from well-conducted clinical trials provide compelling evidence supporting dosing regimens or reconsideration of treatment approach (e.g., dose, frequency, route of administration, timing, etc.), and should be integrated in the framework as experience is acquired.

SUMMARY

Combating an urgent public health pandemic threat like COVID-19 requires rapid and efficient identification of effective and safe treatments targeting the infecting pathogen. Clinical pharmacology information, including mechanism of action and antimicrobial activity, PK and PD knowledge gained from preclinical experience, and any known PK and PD characteristics of the drug or biologic in humans, should be leveraged for dose justification in a pandemic setting. A coordinated effort should be made on a global, collaborative level to develop cohesive systems for integration of these data and frameworks for facilitating dosing regimen optimization in emergency situations. The experience, history, and lessons learned with Animal Rule products offer a framework to efficiently leverage known clinical pharmacology information for dosing regimen design, enabling therapeutic preparedness during pandemics.

Funding. No funding was received for this work.

Acknowledgments. The authors would like to thank Kellie S. Reynolds and Shiew-Mei Huang for their review of this manuscript.

Conflict of Interest. The authors declared no competing interests for this work.

Disclaimer. The opinions expressed in this paper are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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