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ScienceTalk

Virtual patients for therapeutic drug trials

Using modelling, different doses of drugs can be given to 'patients' to test effectiveness

Using computer software and virtual patients, drug trials can now also be conducted outside laboratories, an approach that has been endorsed by drug regulators in the United States, Europe and Japan. PHOTO: REUTERS

Eric Chan and Eleanor Cheong

In the science fiction movie Ready Player One, the virtual world was an escape from the harsh realities of the real world, an oasis where individuals can go anywhere, do anything and be anyone.

In today's world, could virtual simulation technologies be extended to high-risk human research, such as drug trials, on people?

DRUG TRIALS: THE CURRENT APPROACH

Therapeutic drug trials involving human volunteers have been the gold standard in validating the safety and efficacy of new or existing treatments.

However, research involving human subjects is risky. Hence, human clinical trials are conducted under stringent regulatory review and approval. As a result, studies in vulnerable subgroups such as the elderly, pregnant women, or children are often restricted.

Even when performed successfully, clinical trials are often limited to describing the "average" response to therapies in a large group of patients enrolled. By generalising group outcomes, a one-size-fits-all treatment solution results.

But no two people are the same.

The reality is that many therapies administered to a large group of patients tend to work better for some people than others.

Recent advances in diagnostic capabilities and the growing availability of health data have given us unprecedented glimpses into the unique profile of each patient as genetically, physiologically, and pathologically distinct individuals.

We would also expect these patients to be given different combinations of medications based on their underlying medical conditions.

This recognition that individuals are unique is driving the paradigm shift to precision medicine, which aims to deliver the right medication, at the right dose, to the right patient and at the right time.

VIRTUAL PATIENTS

Modelling and simulation allow clinical research to be reimagined for individualised therapy, while maximising therapeutic benefits and minimising risks.

Organ size, tissue blood flow and organ function are just a few of the many known physiological variables defining an individual.

Differences among individuals arise because these variables are altered across different ethnic groups, life stages or disease states. With a growing understanding of how these parameters are altered, various virtual patient populations can be created.

Physiologically based pharmacokinetic (PBPK) modelling uses mathematical representations of the biological system to quantify how such variability in health and disease affects drug exposure in the human body and its associated therapeutic outcome.

Ensuring that drug levels fall within a safe and efficacious range is one of the primary goals of treatment. Using PBPK modelling, our laboratory at the National University of Singapore (NUS) has recently looked at the complex drug-drug interactions between rivaroxaban and amiodarone, two medications which are frequently co-administered in patients with atrial fibrillation – a condition characterised by an irregular and often rapid heart rate that can increase the risk of stroke, heart failure and other heart-related complications.

Based on the simulation results, dosage adjustments of rivaroxaban are recommended to mitigate its bleeding risk while preserving its anti-coagulation effect in patients with both atrial fibrillation and renal impairment. Our recommendation was published in the Journal Of The American College Of Cardiology.

PBPK MODELLING COMES OF AGE

In recent years, the emergence of user-friendly software platforms which allow the integration of human population databases and drug attributes have greatly facilitated the widespread adoption of PBPK modelling by academia, the pharmaceutical industry and regulatory agencies. The regulatory endorsement has been emphatic as the United States Food and Drug Administration (FDA), the European Medicines Agency and the Japanese Pharmaceuticals and Medical Devices Agency have emphasised the necessity of this shift towards precision dosing based on modelling.

This momentum has also been instrumental in catalysing industry uptake of PBPK modelling.

Survey results reveal that out of the 85 new drugs that were approved by the FDA between January 2013 and August 2016, a total of 18 medications included PBPK model-informed guidelines on their product labels.

For instance, in the development of ibrutinib – which is for the treatment of patients with mantle cell lymphoma, a type of cancer – Janssen Pharmaceuticals applied PBPK modelling to guide dosing in the presence of drug-drug interactions.

In the real world, we envision a landscape where healthcare and technology will converge in perfect synergy to direct and inform precision medicine – not just for subsets of patients, but for individual patients. Each person will have a virtual self, based on their genes and characteristics, who can participate in virtual clinical trials on behalf of the real person.

THE FUTURE

In Ready Player One, a dystopian future was painted where avatars were used to retreat from the real world.

In the real world, we envision a landscape where healthcare and technology will converge in perfect synergy to direct and inform precision medicine – not just for subsets of patients, but for individual patients.

Each person will have a virtual self, based on their genes and characteristics, who can participate in virtual clinical trials on behalf of the real person. Before we test or treat an actual patient, we will treat his avatar and assess drug response so as to come up with dosages that will maximise the benefits of treatments, while minimising side effects.

About the writers

Associate Professor Eric Chan is a pharmaceutical scientist and the Dean's Chair in the Department of Pharmacy, Faculty of Science, National University of Singapore (NUS). He is a council member of the International Society for the Study of Xenobiotics, which is the study of chemical compounds such as consumer products and food ingredients, environmental pollutants, drugs or pesticides that are foreign to a living organism. He is also an adjunct principal investigator at the Singapore Institute for Clinical Sciences, as well as a platform lead under the Innovations in Food and Chemical Safety Programme at the Agency for Science, Technology and Research.

Miss Eleanor Cheong is Prof Chan's PhD student at NUS. Her research project focuses on the optimisation of pharmacotherapy in atrial fibrillation and metastatic castration resistant prostate cancer using PBPK modelling.