CERTARA

Assessing Drug-Smoking Interactions

Physiologically-based modeling and simulation helped a drug sponsor anticipate the impact of smoking cessation on drug exposure levels and toxicity risk, avoiding the need for a costly clinical trial

Background

Schizophrenics are often heavy smokers, which can affect the metabolism of other drugs. With smoking prohibited in hospitals across most countries, a global pharmaceutical company developing a new antischizophrenia drug faced concerns about potential increases in drug exposure and ensuing toxicity should there be a need for hospitalization.

Elimination of the new drug candidate was mediated almost exclusively by the enzyme cytochrome P450 1A2 (CYP1A2). Cigarette smoking induces CYP1A2 in a dose-dependent manner; heavy smoking has been shown to dramatically increase the clearance of drugs metabolized by that pathway, such as caffeine.[1]

Challenge

Given the potential for abrupt changes in smoking habits brought about by hospitalization, the sponsor sought to understand whether it would be possible to keep patients' exposures within the therapeutic window through appropriate clinical management. In particular, they wanted to evaluate whether sudden smoking cessation, and the resulting loss of CYP1A2 induction, might cause a spike in plasma concentration that could increase risk of an adverse drug reaction (ADR).

Excess risk would make the drug candidate non-developable. Evaluation of this potential go/no go decision point through additional clinical testing would cost several million dollars and extend development by a one- to two-year time frame. A model-based solution was sought.

Solution

The sponsor worked with Certara scientists to better understand likely exposure levels of their drug in smokers, especially following abrupt cessation of smoking.

Challenge

The sponsor wanted to evaluate whether sudden smoking cessation in patients with schizophrenia, and the resulting loss of CYP1A2 induction, might cause a spike in plasma concentration for a new antischizophrenia drug that could increase the risk of an adverse drug reaction.

Solution

Certara scientists performed simulations to predict plasma concentrations of the drug in patients before and after smoking cessation; they then compared the simulated plasma concentrations to a range of possible adverse drug reaction thresholds.

Benefit

The PBPK modeling and simulations showed that adverse drug reaction were unlikely to occur and, if observed, they would be clinically manageable.

The sponsor developed a physiologically-based pharmacokinetic (PBPK) model showing the effect of smoking level on CYP1A2-mediated drug clearance based on published data for two drugs metabolized through that pathway. Simulations using the model reliably predicted clearance values and steady-state and trough plasma concentrations consistent with published observations. The results successfully predicted exposures in smokers and nonsmokers, as well as smokers before and after they stop smoking.

Certara worked with the sponsor to perform dose simulations to predict steady-state and trough concentrations of the candidate drug in smokers before and after smoking cessation. They compared the simulated plasma concentrations to a range of possible ADR thresholds.

Benefit

The PBPK modeling and simulations showed that while there was a small likelihood of ADRs in a small percentage of patients, this would be clinically manageable.

Impact

Evaluation of this go/no go decision point using PBPK modeling and simulation took a few weeks, saving as much as two years and 1–2 million dollars had a conventional clinical evaluation been performed.

References

1. Tantcheva-Poór I, Zaigler M, Rietbrock S, Fuhr U. Estimation of cytochrome P-450 CYP1A2 activity in 863 healthy Caucasians using a saliva-based caffeine test. *Pharmacogenetics*. 1999 Apr;9(2):131-44. PMID: 10376760.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit www.certara.com or email sales@certara.com.

© Copyright Certara 2016

CS Jun 2016 v2 080316