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CSI Simcyp: How PBPK Models Provided Insight into a Fatal Drug Poisoning

Scientists at the Aarhus University in Denmark used the Simcyp Simulator to support a forensic toxicological assessment of a fatal drug poisoning case.

Background

A 34 year old Caucasian male was found dead at home, and nothing in the case pointed to either suicide or a crime having occurred.[1] Neither the cause nor the manner of death could be determined from the autopsy. The deceased had taken daily medication including venlafaxine (VEN).

VEN is an antidepressant whose side effects include cardiotoxicity and serotonin toxicity.[2] The pharmacologically active metabolite of VEN is O-desmethylvenlafaxine (ODV).[3] VEN is eliminated primarily by metabolism by cytochrome P450 (CYP) enzymes including CYP2C9, CYP2C19, CYP2D6, and CYP3A4.[4-6] VEN elimination shows high interindividual variability. Certain CYP-isoforms are polymorphic and individuals lacking acitvity are termed "poor metabolizers" (PMs). Individuals lacking CYP2C19 or CYP2D6 activity (PMs) have been shown to be in increased risk of higher VEN concentrations, and thus at higher risk of VEN side effects.[5]

Challenge

Aarhus University scientists sought to determine the causes of this case of an unintended fatal drug poisoning. Specifically, they wanted to know if the high VEN concentration in the victim could have been due to lack of activity of both CYP2C19 and CYP2D6.[1]

Solution

Post-mortem toxicological screening revealed a high blood concentration of VEN as well as an exceptionally low ratio of ODV/VEN. The victim's death was likely due to accidental poisoning with a combination of VEN, oxycodone, and ethanol.

To examine whether a combined PM status for CYP2C19 and CYP2D6 could significantly contribute to the high VEN concentration and low ODV/VEN ratio, they performed physiologically-based pharmacokinetic (PBPK) simulations using the Simcyp Simulator version 11.00. This PBPK platform links

Challenge

Aarhus University scientists sought to determine the causes for toxic levels of medication in the case of an unintended fatal drug poisoning.

Solution

They used mechanistic pharmacokinetic simulations to determine whether reduced metabolic capacity caused potentially toxic venlafaxine (VEN) concentrations in the poisoning victim.

Benefit

Pharmacokinetic simulations suggested that a lack of metabolic capacity due to missing CYP2C19 and CYP2D6 activity could have contributed to the fatal drug poisoning.

in vitro data to *in vivo* ADME (absorption, distribution, metabolism, and excretion) to predict pharmacokinetic/pharmacodynamic (PK/PD) outcomes. The input parameter values for the PBPK models for the elimination of VEN and ODV were derived from the literature.

The simulations used the minimal physiologically-based model. By using virtual populations, the investigators were able to probe the population's average VEN and ODV concentrations and assess interindividual PK variability as well as the importance of different CYP phenotypes. The Simcyp Simulator's standard virtual population is comprised of healthy volunteers aged 18-65 with equal numbers of males and females. This default population has a distribution of metabolic CYP phenotypes that reflects a healthy Northern European population. To determine the impact of various CYP phenotypes, the default virtual population was modified to consist of various combinations of only CYP2C19 or CYP2D6 extensive metabolizers/poor metabolizers. The virtual populations were dosed as the deceased, 150mg VEN twice daily, to reach steady state concentrations.

Simulated VEN and ODV concentrations and ODV/VEN ratios were compared to reported concentrations from therapeutic drug monitoring (TDM). The simulations revealed that the combined lack of CYP2D6 and CYP2C19 activity likely caused the very low metabolite ratio and the high VEN concentration observed in the victim. Additionally, concurrent medications and prerenal impairment triggered by dehydration may have also contributed to the victim's toxic VEN concentration.

Genetic analysis was performed to corroborate the VEN simulation results. Genotyping results indicated that the victim carried alleles of both CYP2C19 and CYP2D6 corresponding to a combined PM status. Only one out of 700 individuals in a Caucasian population lack activity for both enzymes. The combination of having a rare genotype that caused reduced metabolic capacity, being on a high dose of VEN, taking other medications concurrently, and prerenal impairment formed a perfect storm that resulted in fatal drug toxicity for the victim.

Benefit

Based on the potentially lethal consequences of reduced metabolic capacity, performing TDM on patients with low CYP2C19/CYP2D6 activity might help prevent adverse reactions occurring from typically prescribed doses of VEN.

Impact

This fatal drug poisoning case shows the potential utility for using PBPK models to inform forensic toxicological assessments. Due to PBPK models' ability to reflect a wide range of dosing scenarios and intrinsic/extrinsic patient factors, they are an ideal tool for helping determine the unsolved mechanisms behind fatal poisoning cases.

References

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