

Pharmacokinetic interactions between glimepiride and rosuvastatin in healthy Korean subjects: does the SLCO1B1 or CYP2C9 genetic polymorphism affect these drug interactions? Observations and introspection of the bioanalysis

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Dear editor

The topic of polymorphism in drug metabolizing enzymes and drug transporters with their impact on pharmacotherapy is of great interest. The clinical relevance depends on the vectorial movement, the therapeutic index of the substrates and inherent interindividual variability.¹ With respect to the variability, various polymorphisms associated with the drug transporters have been reported that led to the alteration in the pharmacokinetic and pharmacodynamic profile of the drugs.² Many preclinical and clinical studies have provided the evidence for the application of genetic information for the development of individualized therapies.³

Recently, Kim et al demonstrated a well-planned and meticulously executed clinical investigation to understand the role of SLCO1B1 or CYP2C9 genetic polymorphism on the pharmacokinetics of glimepiride and rosuvastatin in healthy Korean subjects.⁴ Most importantly, the pharmacokinetic interaction study consisted of two parts: parts 1 and 2. Part 1 was designed to evaluate the effect of rosuvastatin on the pharmacokinetics of glimepiride and part 2 was designed to determine the effect of glimepiride on the pharmacokinetics of rosuvastatin. Blood samples were collected at predetermined time points and samples were analyzed using liquid chromatography-mass spectrometer to determine the drug concentration in the plasma samples.⁴

The intent of this letter is to highlight the concerns related to the sample processing method adopted by the authors for bioanalysis. For analysis of rosuvastatin and *N*-desmethyl rosuvastatin, the authors took 50 µL of plasma and mixed with 10 µL of valsartan, an internal standard (100 ng/mL in 50% acetonitrile).⁴ The mixture was centrifuged, followed by the collection of supernatant, which was evaporated till dryness and reconstituted in 200 µL of 50% acetonitrile for analysis.⁴ From the process detailed by the authors, it is evident that the authors wanted to deproteinize the plasma samples using 50% acetonitrile containing the internal standard. However, the concern is the amount and concentration of acetonitrile used for protein precipitation. An ideal amount for organic solvents (at 100% concentration) used for deproteinization should be more than 3–4 volumes of the plasma sample to achieve optimum precipitation.^{5,6} However, the authors have used only 10 µL of organic solvent (one-fifth of the plasma volume)

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at 50% concentration⁴, which raises the concern regarding the insufficient protein precipitation and the amount recovered for the subsequent process. The same sample extraction process has been adopted for glimepiride as well.

Yet another concern is the column temperature mentioned in the bioanalytical method to be 500°C,⁴ which is expected to be too high for any kind of chromatographic columns. Do the authors want to say 50°C or are they indicating about the ion-source temperature of the mass spectrometer as 500°C? Although the authors have tried to understand the mechanistic aspects of genetic polymorphism on pharmacokinetic interaction of rosuvastatin and glimepiride, the bioanalytical method adopted for pharmacokinetic studies needs further clarification.

This communication was prepared to promote an exchange of thoughts on a topic of great interest in genetic polymorphism and pharmacokinetic interactions.

Disclosure

The authors report no conflicts of interest in this communication.

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Author's reply

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Dear editor

First of all, we would like to thank Thakkar and Dash for their interest in our paper “Pharmacokinetic interactions between glimepiride and rosuvastatin in healthy Korean subjects: does the SLCO1B1 or CYP2C9 genetic polymorphism affect these drug interactions?” Regarding their concerns about the sample processing of rosuvastatin and *N*-desmethyl rosuvastatin, they seem to have misunderstood because detailed contents were missed. As mentioned by Thakkar and Dash, higher amounts of organic solvents are used for deproteinization. Before the mixture of plasma and internal

standard was centrifuged, we added 800 μ L of 0.1% formic acid – diethyl ether (1:7, v/v) to deproteinize. We consider that our sample extraction process for rosuvastatin and *N*-desmethyl rosuvastatin analysis was appropriate because organic solvents were added at more than 10 times the volume of the plasma sample.

Similar to the sample processing of rosuvastatin and *N*-desmethyl rosuvastatin, 800 μ L of 0.1% formic acid – diethyl ether (1:7, v/v) were added to the mixture with plasma and internal standard for glimepiride analysis, and then the mixture was centrifuged. After centrifugation, 100 μ L of supernatant was diluted with 100 μ L of water, and 10 μ L of the resultant solution was injected directly into the column heated at 40°C not 500°C. Unfortunately, we confirm that the column temperature for glimepiride assay was a typo. We are pleased to be able to correct our paper.

Disclosure

The authors report no conflicts of interest in this communication.

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