Extended Abstract Journal of Clinical and Bioanalytical Chemistry 2020
Vol.4 No.2

Analytical-2016 : Utility of hair like microsampling for rodent pharmacokinetic considers: Comparison of tail-vein seeps to jugular vein cannula testing-J Wang- Sanofi Genzyme

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Feng-Liao-Chang-Wei-Kang (FLCWK) is a customary Chinese patent medication that for the most part comprises of Daphniphyllumcalycinum roots and Polygonumhydropiper. As a complex containing a few sorts of flavonoids, FLCWK affects the medication digestion catalyst P450 3A4(CYP3A4) and atomic receptors. This examination means to investigate the impacts of FLCWK on CYP3A1 (CYP3A4's homolog in rodents) in rodents and to decide if FLCWK could take an interest in the procedures of hPXR-and hCAR-interceded transactivation of CYP3A4. The impacts of FLCWK on CYP3A1 mRNA, protein articulation and reactant action levels in Sprague-Dawley(SD) rodent liver tissues were identified utilizing constant PCR, western blotching and high performance liquid chromatography (HPLC) examines. The impacts of hPXR and hCAR on CYP3A4 transcriptional movement were inspected utilizing luciferase column quality measures. Further investigation of FLCWK on the CYP3A4 quality articulation interceded by PXR pathway was explored by transient transfection of PXR siRNA. This examination found that FLCWK could fundamentally expand the CYP3A1 mRNA quality and protein articulation levels and CYP3A1 movement in SD rodents. In PXR-CYP3A4 co-transfected cells, FLCWK could altogether actuate CYP3A4 luciferase action interceded by PXR. PXR-knockdown (transfected with siPXR build) diminished the CYP3A4 mRNA level than in the control cells transfected with relating vector. Taken together, these discoveries recommend that FLCWK could essentially up-manage CYP3A4 levels by means of the PXR-intervened pathway. This impact ought to be contemplated to anticipate any potential medication tranquilize associations among FLCWK and other coadministered drugs. Serial sampling methods have been used for rat pharmacokinetic (PK) studies for over 20 years. Currently, it is still common to take 200-250 µL of blood at each timepoint when performing a PK study in rats and using serial sampling. While several techniques have been employed for collecting blood samples from rats, there is only limited published data to compare these methods. Recently, microsampling (≤ 50 µL) techniques have been reported as an alternative process for collecting blood samples from rats. In this report, five compounds were dosed orally into rats. For three proprietary compounds, jugular vein cannula (JVC) sampling was used to collect whole blood and plasma samples and capillary microsampling (CMS) was used to collect blood samples from the tail vein of the same animal. For the two other compounds, marketed drugs fluoxetine and glipizide, JVC sampling was used to collect both whole blood and blood CMS samples while tail-vein sampling from the same rats was also used to collect both whole blood and blood CMS samples.For the three proprietary compounds, the blood AUC as well as the blood concentration-time profile that were obtained from the tail vein were different from those obtained via JVC sampling. For fluoxetine, the blood total exposure (AUC) was not statistically different when comparing tail-vein sampling to JVC sampling, however the blood concentration-time profile that was obtained from the tail vein was different than the one obtained from JVC sampling. For glipizide, the blood AUC and concentration-time profile were not statistically different when comparing the tail-vein sampling to the JVC sampling. For both fluoxetine and glipizide, the blood concentration profiles obtained from CMS were equivalent to the blood concentration profiles obtained from the standard whole blood sampling, collected at the same sampling site.

The data in this report provide strong evidence that blood CMS is a valuable small volume blood sampling approach for rats and that it provides results for test compound concentrations that are equivalent to those obtained from traditional whole blood sampling. The data also suggest that for some compounds, the concentration-time profile that is obtained for a test compound based on sampling from a rat tail vein may be different from that obtained from rat JVC sampling. In some cases, this shift in the concentration-time profile will result in different PK parameters for the test compound. Based on these observations, it is recommended that a consistent blood sampling method should be used for serial microsampling in discovery rat PK studies when testing multiple new chemical entities. If the rat tail vein sampling method is selected for PK screening, then conducting a bridging study on the lead compound is recommended to confirm that the rat PK obtained from JVC sampling is comparable to the tail-vein sampling.

This work is partly presented at 20th world congress on clinical and bioanalytical chemistry on October 30-31,2019 at Londan (UK)

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