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Investigation of possible pharmacokinetic interaction between ivabradine and carvedilol in rats using high performance liquid chromatography/mass spectroscopy

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Ivabradine is a new hyperpolarization-activated cyclic nucleotide-gated channel blocker. It has been approved by the FDA in 2015 in management of stable angina and congestive heart failure. The aim of this study was to investigate the possibility of pharmacokinetic interaction of a proposed combination of ivabradine and the β -blocker carvedilol in rats using spectroscopy technique. A simple, rapid and sensitive method for validation and determination of ivabradine and carvedilol in the rat's plasma was developed using HPLC/MS. The method was successfully developed and validated in terms of linearity, precision and accuracy which were within the values accepted by EMEA and ICH. Ivabradine and carvedilol were given both intravenously and orally each alone and as oral combination to fasted Sprague-Dawley rats. Blood samples were withdrawn on scheduled time intervals up to 36 hours and analyzed for each drug. Both compartmental and non-compartmental kinetic analysis was performed on plasma level-time data and the kinetic parameters were calculated from non-compartmental analysis. Results showed significant increase in bioavailability of both drugs in combination (94% for carvedilol and 58% for ivabradine). Also, C_{max} was changed significantly from by 165% for carvedilol and 56% for ivabradine when given in combination. There was also a significant decrease in elimination of both drugs expressed as 48% decrease in clearance and 41% increase in the half-life for carvedilol and 32% decrease in clearance and 37% increase of the half-life of ivabradine when given in combination. These changes suggested an interaction on metabolic function of the liver on both drugs by enzyme inhibition. Also, the rate of absorption of ivabradine was slowed by concomitant administration of carvedilol suggesting an interaction on absorption level. In conclusion, a significant kinetic interaction occurred when ivabradine was given orally with carvedilol which makes dose adjustment of both drugs of much importance.

Biography

Saif S Abbas is pursuing his Master's degree in Pharmaceutics/Pharmacokinetics at Al-Ahliyya Amman University in Jordan. He has completed his graduation from Faculty of Pharmacy and Medical Sciences in Al-Ahliyya Amman University/Jordan in 2013. He worked as a Senior Pharmacist in retail pharmacies and drug stores in Amman/Jordan.

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