Research & Reviews: Journal of Hospital and Clinical Pharmacy

Comparative Pharmacokinetic Study of Ledipasvir after Single Dose Using Novel Methodology

Saad A Alkahtani
Dean, College of Pharmacy, Najran University, Saudi Arabia, saaalkahtani@nu.edu.sa

Extended Abstract

Abstract

Aim of work

Therefore, pharmacokinetic study of LEDV was investigated using novel validated highly sensitive sensor obtained in our laboratories and comparing the results with the reported results obtained by using LC/MS/MS technique.

Keywords

Ledipasivir, hepatitis C, Viral RNA, metabolism

Background

Ledipasivir (LEDV) is a direct acting antiviral used for treatment of hepatitis C, especially in GT4 infection via termination of HCV proliferation inside the body and has the advantage of dose reduction compared to the other traditional antiviral agents. Dose adjustment is highly important for improving the efficacy of therapy and decreasing both the side effects and patient health's care cost. To obtain clinically trusted data, we should use highly sensitive and selective bio-analytical techniques, capable of using small sample volumes, with no interferences from endogenous or exogenous compounds. Ledipasvir is a non-structural protein 5A (NS5A) replication complex orally available inhibitor of the hepatitis C virus (HCV), with potential activity against HCV. Ledipasvir binds to and inhibits the action of the NS5A protein after oral administration and after intracellular absorption. This leads to disruption of the complex replication of viral RNA, blockage of development of HCV RNA, and inhibition of viral replication. NS5A, a zinc-binding, proline-rich hydrophilic phosphoprotein, plays an essential role in the synthesis of HCV RNA. HCV is a small single-stranded, enveloped RNA virus belonging to the family Flaviviridae. Ledipasvir is a direct antiviral drug used in combined therapy to treat chronic hepatitis C, an infectious liver disease caused by hepatitis C virus infection. HCV is a single-stranded RNA virus classified into nine distinct genotypes, with Genotype 1 being the most prevalent in the United States, affecting 72 per cent of all chronic HCV patients. Chronic hepatitis C treatment options have dramatically improved since 2011, with the introduction of Direct Acting Antivirals (DAAs) such as ledipasvir. More precisely, ledipasvir is an inhibitor of the 5A non-structural hepatitis C virus, which is necessary for the replication and assembly of HVC virions viral RNA. Ledipasvir is a benzimidazole analog used in conjunction with sofosbuvir (under the trade name Harvoni) to treat chronic genotype 1 hepatitis C infection. This has a role as an antiviral medication and a protease inhibitor for hepatitis C. Treatment with ledipasvir is used after 12 weeks of routine treatment in order to treat, or maintain, a persistent virologic reaction (SVR). SVR and HCV eradication is associated with important long-term health benefits including decreased liver injury, increased quality of life, decreased prevalence of hepatocellular carcinoma and reduced all-cause mortality. Treatment of specifically acting antivirals such as ledipasvir is associated with very minor side effects, with headache and fatigue the most severe. Although its exact mechanism of action is unclear, it is postulated to prevent the NS5A hyperphosphorylation necessary for the development of viral protein. This is selective against genotypes 1a, 1b, 4a, and 5a and against genotypes 2a and 3a of HCV with reduced development. Ledipasvir and other direct acting antivirals are very effective treatment options for hepatitis C, as they pose a strong barrier to resistance growth. This is a substantial improvement relative to HCV drugs that target other viral enzymes such as protease, for which rapid resistance growth has proved to be a major cause of therapeutic failure. Lack of severe side effects and short treatment length is a major improvement over older interferon- and ribavirin-based regimens, which were hampered by infusion site responses, decreased blood counts and neuropsychiatric effects. Since 2014, ledipasvir has been available as a fixed dose combination drug for the treatment of chronic hepatitis C with sofosbuvir.

Approved by the FDA in October 2014, Harvoni is recommended for the treatment of HCV genotypes 1, 4, 5 and 6 with or without ribavirin, depending on the extent of liver damage or cirrhosis. After 12 weeks of therapy, ledipasvir and sofosbuvir as the combination drug Harvoni have been shown to produce an SVR of 93 to 99 percent when combined. Its use in treating HCV in patients co-infected with HIV has also been effective. Ledipasvir is an inhibitor of the NS5A protein Hepatitis C Virus (HCV) necessary for the replication and assembly of HCV virions by viral RNA. While it is unclear about its exact mechanism of action, it is postulated to prevent the hyperphosphorylation of NS5A necessary for viral growth. A single oral dose of [14C]-ledipasvir of 90 mg, mean cumulative recovery of [14C]-radioactivity in feces and urine was around 87%, with much of the radioactive exposure obtained from feces (around 86%). Unchanged ledipasvir excreted in stool accounted for an average of 70 percent of the administered dose and 2.2 percent of the dose was in the oxidative metabolite M19. In vitro, human CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 reported any observable ledipasvir metabolism. Proof of the slow oxidative metabolism was found by an unexplained mechanism.

Method

Six volunteers had fed prohibited for 12 h before the study but the water was freely available. The blood samples (3.0 mL) were collected from a forearm vein into heparinized polyethene tubes at 0.00 (pre-dose), 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 6, 10, 13, 18, 24 h after oral administration of Harvoni®400/90 mg tablets. The samples were immediately centrifuged at 4000 rpm for 10 min. The plasma was stored at −80°C until analysis. The pharmacokinetic parameters for LEDV were estimated using the validated moment analysis software.

Results

The methodology was fully validated according to FDA guidelines with respect to linearity, accuracy, precision, recovery, selectivity. The sensitivity of the method was found to be sufficient for accurately measuring the main pharmacokinetic parameters for LEDV. The validated methodology was successfully applied to determine LEDV in human plasma after oral administration of a tablet containing 400/90 mg SOF/LED. Following absorption, LEDV reaches maximum plasma concentrations (T max) at 4.23± 2.09 h post-dose and is eliminated with (t½) of 31.1± 2.6 h. The Cmax was 183.7±25.6 ng/mL, while AUC 0-t and AUC 0-∞ were 3709±1033 and 4201± 2345 ng/mL.h, respectively. The elimination rate constant (Ke) and clearance (CL) were 0.026± 0.0001 h-1 and 0.034±34.6 mg/(ng/mL h), respectively. Our study proved that there was no significant difference in pharmacokinetic parameters with other reported data.