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Research Article

Impact of a Moderate-Fat Meal on the Bioavailability of Ribavirin in Patients with Hepatitis C

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ABSTRACT

Introduction: Ribavirin is a nucleoside analog used in hepatitis C therapy. The bioavailability of oral ribavirin is increased by co-administration with high-fat food. Therefore, ribavirin manufacturers recommend taking the drug with food. However, moderate fat meal effect on Ribavirin bioavailability is yet not established.

Objectives: To compare the bioavailability of ribavirin in patients with hepatitis C virus (HCV) genotype 4 (G4), either taken after a moderate-fat meal or in fasting state.

Methods: We conducted a crossover, randomized, open-label study including 82 naïve patients (49 women and 33 men, mean age 53.40±1.39 years) with chronic hepatitis C at King Abdulaziz Medical City, Riyadh, Saudi Arabia, from 2012 to 2014. Patients received 600 mg of oral ribavirin on two occasions at least three weeks apart of washout period: first in a fasting state and second time after a moderate fat breakfast containing ≃18 g fat. Participants in both states underwent a pharmacokinetic profile analysis at 0.5, 1.0 and 2.0 hours after each dose.

Results: Compared with the fed state, ribavirin plasma concentrations were significantly higher in the fasting state at 0.5 hours and 1 hour post-dose(p=0.004 and 0.021, respectively), and significantly lower at 2 hours post-dose (p=0.011). However, the area under the curve for ribavirin concentrations within the first 4 hours post-dose ($AUC_{0\text{-}4h}$) was not different between the two states (p=0.956).

Conclusions: Among adult patients with HCV G4, there was no significant difference in ribavirin bioavailability between fasting and fed (≃18-gram fat meal) states, thus for better patients adherence we recommend that physicians consider patient convenience in regards to the timing of ribavirin oral intake with or without food.

Keywords: Hepatitis C virus, Genotype 4, Ribavirin, Bioavailability, Saudi Arabia

Introduction

Almost 70 million worldwide people are infected with Hepatitis C virus (HCV). HCV genotype 4 represents more than 80% of HCV infections in the Middle East and Africa [1].

The prevalence of HCV in Saudi Arabia is thought to be 1%with genotype 4 accounting for 64.5% [2].

HCV Treatment goals are to eradicate and cure HCV infection, prevent liver cirrhosis/decompensation, Hepatocellular Carcinoma, and death.

Evaluation of liver disease severity/fibrosis should be done prior to initiation of treatment since treatment and post-treatment surveillance for hepatocellular carcinoma are adapted in cirrhotic patients. Evaluation is applied through fibroscan (transient elastography) and/or liver biopsy being reserved for cases of uncertainty or possible additional etiologies [3].

Ribavirin /ri·ba·vi·rin/ is a purine nucleoside analog with a modified base and D-ribose sugar, it inhibits the replication of a wide range of RNA and DNA viruses. The antiviral mechanism of ribavirin is incompletely understood, but it relates to the alteration of cellular nucleotide pools and the inhibition of viral messenger RNA synthesis [4].

Oral ribavirin in combination with pegylated interferon (IFN) alfa-2a or IFN-2b is the previous standard treatment for chronic HCV infection with ribavirin dose being weight dependent and IFN standardized. Patients ≤75 kg: 400 mg PO qAM, 600mg PO qPM and for patients >75 kg: 600 mg PO q12hr plus 3 million IU three times weekly SC for 24-48 weeks for treatment-naïve patients [5-7].

Upon oral administration, nucleoside transporters actively take up ribavirin in the proximal small bowel; overall, bioavailability of orally taken ribavirin averages approximately 46% [7,8].

Plasma concentrations peak at approximately 0.8 μg/ml after a single dose of 600 mg ribavirin and 3.7 μg/ml after multiple similar doses. Ribavirin then accumulates in the plasma, and a steady state plasma concentration of the drug is reached by approximately 4 weeks of ribavirin therapy with a half life of 298 hours (approximately 12 days). The apparent distribution of ribavirin is large (~10 L/kg) owing to its cellular uptake in to nonplasma compartments [6,8].

The elimination of the drug occurs through hepatic metabolism as well as renal excretion of ribavirin and its metabolites [7].

Ribavirin levels are altered by food intake. Administration of the drug in a fed state lead to an increase of 70% in both Cmax and the area under the curve (AUC), and an increase in Tmax (mean = 3.3 hours), relative to administration without food [9].

Lean body weight was the only covariate that had a clinically significant influence on ribavirin pharmacokinetics, namely its clearance. A standard meal did not affect ribavirin bioavailability, however, a high-fat meal increased ribavirin bioavailability by 46% compared to the fasting state [10].

To the best of our knowledge, no pharmacokinetic studies have been performed previously regarding the effect of a moderate-fat diet on ribavirin bioavailability among patients with HCV infection in Saudi Arabia. Since moderate fat meal is the ideal meal physicians advice patients to adhere to especially in overweight predominant population and also ribavirin is recommended to be taken with food, we have aimed to asses moderate fat meal (usual meal most people consume) effect on ribavirin bioavailability, because optimizing ribavirin administration may increase the sustained virological response (SVR) leading to a better response to HCV therapy and whenever Ribavirin is administered for any indication other than HCV thus better outcome [1].

Methods

A crossover, randomized prospective, open-label study was conducted in the hepatology division of the hepatobiliary sciences department in King Abdul-Aziz Medical City (KAMC), Riyadh, Saudi Arabia between 2012 and 2014.

The optimal sample size was predetermined using a paired sample t-test in SAS version 9.2 (SAS Institute Inc., Cary, NC; 2007). We found that a sample size of 113 would have 80% power to detect a difference in means of -0.290. This model assumes a standard deviation of differences of 1.088, using a paired t-test with a 0.050 two-sided significance level.

The 82 HCV G4 patients (49 women and 33 men) included in this trial are treatment-naïve newly diagnosed through Anti-HCV Antibodies and HCV RNA. Each served as his/her own control. Aged 18-70 years. Disease stage/liver fibrosis was assessed using liver biopsy and/or fibroscan (transient elastography).

All patients were provided written informed consent to participate in the study. Ethical and research committee approval was obtained from King Abdullah International Medical Research Center (KAIMRC) before conducting the study.

In each patient, the pharmacokinetic profile of 600 mg oral ribavirin was determined first in a fasting state, and then again at least three weeks later (washout period), in a fed state. Using this approach, the effect of food could be investigated in each participant after 4-5 half-lives had passed (i.e. 3 weeks). The fasting states were defined as self reported 9 hours of fasting. The fed state was defined as a state after an ≈18-g fat breakfast meal, which consisted of a glass of milk (≈5g of fat), half a loaf of Arab bread (≈8g of fat) , and either two triangular pieces of cheese (≈3g each) or one boiled egg(≈5g of fat).

Variables and demographic data were collected from each patient's Electronic Case Report Form.

Ribavirin plasma concentrations were calculated on the basis of either liquid chromatography coupled with mass spectrometry or UV detection, at the Toxicology Lab in King Abdulaziz Medical City laboratory, Riyadh. Ribavirin AUC0-4h was calculated using Bayesian estimation.

In this trial, the covariates that were assessed included race, gender, age, weight, height, lean body weight, body mass index (BMI), HCV RNA status, diabetes mellitus status, creatinine clearance, hematocrit and serum levels of creatinine and albumin. All analyses were performed using NONMEM version V level 1, the FO method and S-PLUS 2000. We used covariate analysis to detect the influences on oral clearance. Using predefined selection criteria plus a clinical significance level of a 20% change in parameter value for backward deletion, covariates were screened for their influence on clearance. A combined sequential zero-order and then first-order process was found to best describe the absorption phase. The influence of meals

on the absorption parameters was investigated and included in the analysis.

Variables gender, diabetes, liver disease stage was summarized as count and percent. Age and BMI were summarized as mean and standard error. Comparison of ribavirin level, and the time effect between fasting and post fed state was done using generalized linear model (GLM). Results were reported as mean, standard error, and p-values. The (AUC_{0-4h}) was compared between the fasting and fed states using a paired t-test. Results were reported as mean difference, standard error, 95%CI and p-value. Mixed model was used for analysing the difference between ribavirin level across gender, diabetes status, BMI, and fibrosis stage. Results were reported as f-value and p-value. Analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

All calculations were performed using the SAS program version 6.12.

Results

Demographic and baseline clinical characteristics of the study cohort

Among the 82 patients with chronic HCV G4 infection, 49 (59.76%) were women and 33(40.24%) were men. The mean age of participants was 53.40±1.39 years, the mean BMI was 28.99±0.65; 33 (40.24%) had type 2 diabetes mellitus. On the basis of liver biopsy and/or fibroscan (transient elastography), the disease stage was F0 or F1 in 56 (68.29%) participants, F2 in 11 (13.41%) participants, F3 in 8 (9.76%) participants and F4 in 7 (8.54%) participants (Table 1).

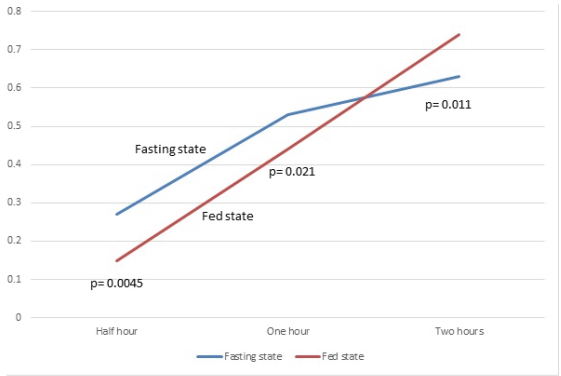
Table 1: Demographic characteristics of the HCV G4 patients.

Variables	Overall n=82
Age mean± SE	53.40± 1.39
Gender n (%)	
Female	49 (59.76)
Male	33 (40.24)
BMI mean± SE	28.99± 0.65
DM n (%)	
Yes	33 (40.24)
No	49 (59.76)
Liver disease stage n (%)	
F0	23 (28.05)
F1	33 (40.24)
F2	11 (13.41)
F3	8 (9.76)
F4	7 (8.54)

Subjects mean age, genders, Body Mass Index (BMI), Diabetes Mellitus (DM) status, and their liver disease stage on the basis of liver biopsy and/or fibroscan.

Ribavirin effects between fasting and fed state over three time points

A statistically significant difference in ribavirin level was observed at different time points after taking the drug, half an hour (p=0.0045) and one hour (p=0.021). By contrast, after two hours, ribavirin levels in the fed state were significantly higher compared with the fasting state, (P = 0.011) (Figure 1).



A comparison of ribavirin level, in (mg/L), between fasting and fed state after Ribavirin oral administration of 600mg. Orange line representing the fed state, and the blue line representing the fasting state with p values after half hour, one hour and two hours.

Figure 1: Ribavirin level comparison in fasting and fed states.

Overall ribavirin effect across gender, BMI, DM and fibrosis

There is no statistically significant difference between ribavirin level regarding gender, DM status, BMI, and fibrosis stage (Table 2).

Fasting and Fed AUC comparison

There was no statistically significant difference observed between fasting and fed (AUC_{0-4h}) (p=0.956) (Figure 2).

Discussion

HCV is a chronic disease requiring treatment and adherence to medications for better outcome. It was already established, in multiple studies, that co-administration of ribavirin with high fat meal increases ribavirin bioavailability by 46% [8-10]. However, we have assessed moderate fat meal effect on ribavirin bioavailability because optimizing ribavirin administration may increase the sustained virological response leading to a better response to therapy thus better outcomes of HCV or for any other indication [1].

Accordingly, our study showed that ribavirin fed state plasma levels were greater than 0.7 mg/l after two hours of oral intake, whereas the fasting state levels did not reach 0.7 mg/l.

Compared from a previous study which showed that ribavirin administration with food will increase Cmax and AUC by 70%; however, in our study the (AUC_{0-4h}) in the fasting and fed states were compared and instead yielded a p value of 0.956 with no statistical significance [9].

A study with similar question in 2006 observed that a standard meal did not affect ribavirin bioavailability; however, a high-fat meal increased bioavailability by 46% relative to the fasting state [10]. A similar result was observed in our study with a moderate-fat meal. Minor differences were found in ribavirin levels between fasting and fed states when compared using the generalized linear model; an increase was observed in the first half hour in the fasting state (revealing more absorption in the first hours of the fasting state) with p values of 0.045, and then a gradual decline was seen after one hour and two hours. However, ribavirin levels showed less absorption

Table 2: Overall Ribavirin Effect with time vs gender, BMI, DM and fibrosis.

Effect	F-value	p-value
Group	1.53	0.219
Time	172.19	<.0001
Group x Time	12.23	<.0001
Gender	2.50	0.118
DM	0.08	0.775
BMI	1.50	0.224
Fibrosis	1.77	0.144

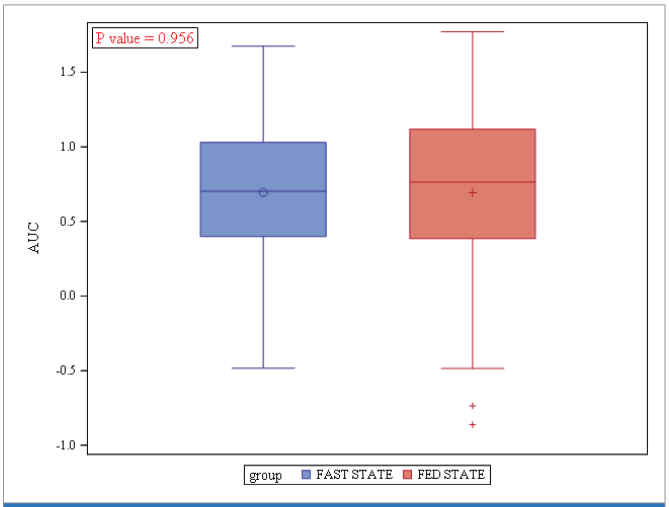


Figure 2: Fasting and Fed AUC comparison.

in the first hour in the fed state compared with the fasting state, probably because fat is absorbed more slowly than ribavirin. The fed state showed a steep incline after two hours, with a significant p value of 0.011 compared with the fasting state probably due to complete food absorption (Figure 1).

The age distribution was mostly middle-age, 53.40±1.39 years. The calculated BMI for these patients was 28.99±0.65 (overweight), which signifies that the majority of HCV population are overweight favoring moderate fat meals compared to high fat meals in terms of dietary advices; increased fat intake in HCV patients who are already overweight as in our patients increases the risk of development of NASH and progressive liver fibrosis which should be avoided by taking less fat in their diet as our study suggests. Fifty-six (68.29%) of these patients were in the early stages of liver disease, (stages F0 and F1), having less likely affecting ribavirin bioavailability and clearance compared to late stages of liver disease. Since moderate fat diet is the ideal meal for an healthy lifestyle to adhere to especially that the mean BMI of the study population is 28.99±0.65 (overweight). Both fasting and fed states will eventually have a Ribavirin level incline after one and two hours of oral administration achieving the net goal of high ribavirin plasma levels thus achieving therapeutic levels.

Sofosbuvir and other new HCV medications have been recently approved with very high efficacy in treatment of HCV.

The limitation of our study is sequence bias: we started with the fasting state, continued with a washout period, and ended with the fed states. However, we confirmed free ribavirin levels through washout periods of more than three weeks. Another limitation is self reporting fasting states by the patients, which may have caused bias in our results, as well as subjects choosing different brands of triangle cheese in the moderate fat breakfast meal altering fat measurement in the meal between subjects leading to minor variations in absorption thus the final results.

In conclusion, there is no significant difference in ribavirin bioavailability in fasting or fed states with moderate fat intake among adult patients with HCV. Thus, we recommend that physicians consider patient's convenience as they take ribavirin for any therapeutic indication and not necessarily taking ribavirin with high fat diet.

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