*Original Article*

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# Pharmacokinetics and safety of single-dose ribavirin in patients with chronic renal impairment

**Samir K. Gupta*, Bhavna Kantesaria, Paul Glue**

*Departments of Drug Metabolism/Pharmacokinetics and Clinical Pharmacology, Merck Research Lab, Kenilworth, NJ, USA.*

**ABSTRACT: This open-label study assessed the pharmacokinetics of a single 400-mg oral dose of ribavirin in 6 healthy volunteers and 18 subjects with varying degrees of renal impairment (mild: creatinine clearance [CLcr] 61-90 mL/min/1.73m$^2$, moderate: CLcr 31-60 mL/min/1.73m$^2$, severe: CLcr 10-30 mL/min/1.73m$^2$, *n* = 6 in each group). Blood and urine samples were collected pre-dose and up to 168 hours post-dose for pharmacokinetic analyses. Compared with control subjects, ribavirin area under the plasma concentration-time curve from time zero to the time of the final quantifiable sample ($AUC_{tf}$) and maximum plasma concentration ($C_{max}$) values were increased, and apparent clearance (CL/F), clearance (CLr), and amount excreted ($A_e$) values were reduced in subjects with renal impairment. Mean ribavirin $AUC_{tf}$ was increased 2- to 3-fold in patients with moderate-severe renal impairment compared with control subjects. Ribavirin CL/F and CLr were significantly correlated with CLcr. Single-dose ribavirin was safe and well tolerated in all subjects. The pharmacokinetics of ribavirin were substantially altered in subjects with stable chronic renal impairment, possibly reflecting changes in ribavirin metabolism associated with renal impairment.**

***Keywords:*** Creatinine clearance, bioavailability, excretion

## 1. Introduction

Ribavirin is a broad-spectrum antiviral agent that is active against a number of RNA and DNA viruses, including hepatitis C virus (HCV) (*1-6*). In patients with chronic hepatitis C, the addition of ribavirin to interferon (IFN) α or pegylated interferon (PEG-IFN) α therapies significantly improves efficacy compared with IFN-based monotherapy regimens, and sustained virologic response rates of 52-56% have been reported in patients receiving PEG-IFN α/ribavirin combination therapy (*7,8*). Ribavirin also forms a component of current protease inhibitor-base triple-therapy regimens with boceprevir or telaprevir (*9-12*).

The single-dose pharmacokinetics of ribavirin have been described in healthy volunteers and in patients with compensated liver disease (*13-17*). These studies reported that ribavirin elimination occurs by both renal and hepatic pathways, with renal processes accounting for only 5-15% of total elimination (*13,15,17,18*). Although renal excretion accounts for a low proportion of total elimination, ribavirin is known to accumulate in patients with renal failure and is not removed by hemodialysis (*19,20*).

Ribavirin treatment is associated with a well-described profile of adverse events, most notably hemolytic anemia, which necessitates hemoglobin monitoring and often results in ribavirin dose modification or use of erythropoietin (*21*). Given the potentially important effects that chronic renal insufficiency has on the pharmacokinetics of ribavirin, this study was conducted to determine the pharmacokinetics, safety, and tolerability of single oral doses of ribavirin in subjects with normal renal function and in those with varying degrees of stable chronic renal insufficiency.

## 2. Materials and Methods

This was an open-label, parallel-group, single-dose study, to assess the pharmacokinetic properties of a single oral 400-mg dose of ribavirin. All medication was provided by Schering-Plough (batch 36524-068; Kenilworth, NJ, USA). This study was conducted in accordance with Principles of Good Clinical Practice and the Declaration of Helsinki. All subjects provided written informed consent to participate in this study, and the protocol was approved by the Research Consultants Review Committee.

### 2.1. *Study population*

Subjects (both males and females), aged 18 to 65 years, with normal renal function or varying degrees of stable

**Address correspondence to:*
Dr. Samir K. Gupta, Clinical Pharmacology & Drug Dynamics, Forest Research Institute, Harborside Financial Center, Plaza V, 185 Hudson St., Jersey City, NJ 07311, USA.
E-mail: Samir.Gupta@frx.com

chronic renal insufficiency were eligible for enrollment. Subjects with normal renal function (creatinine clearance [CLcr] > 90 mL/min) were excluded if they had a history of cardiovascular, neurologic, hematologic, gastrointestinal, cerebrovascular, respiratory, hepatic, or renal disease, or any other disorder requiring physician care. Subjects with evidence of HIV or hepatitis B coinfection, or urinary traces of drugs of abuse, were also excluded. Subjects with compromised renal function (CLcr < 90 mL/min) were excluded if they had significant medical disorders unrelated to their renal disorder that would significantly interfere with their ability to participate in the study. None of the subjects with compromised renal function had chronic hepatitis C infection. For analysis, participants were divided into four groups according to CLcr (based on a 24-hour urinary collection): group I, CLcr > 90 mL/min/1.73 $m^2$ (normal), group II, CLcr 61-90 mL/min/1.73 $m^2$ (mild), group III, CLcr 31-60 mL/min/1.73 $m^2$ (moderate), and group IV, CLcr 10-30 mL/min/1.73 $m^2$ (severe). CLcr was determined using the Cockcroft and Gault equation (*22*).

### 2.2. *Study design*

Participants were fasted overnight and then received a single oral 400-mg dose of ribavirin (2 × 200 mg capsules) with 200 mL of water. Participants continued fasting until 4 hours post-dose. Subjects were discharged from the study center after 48 hours, and subsequent samples were collected on an outpatient basis. Blood samples for determination of plasma ribavirin concentrations were obtained immediately prior to drug administration, then at specified time intervals until 168 hours post-dose. Samples were collected into a syringe. The needle was removed and the contents of the syringe gently placed into a heparinized vacutainer tube that had its top removed. The sample was gently mixed and stored on ice until centrifuged at 4°C at 1,000 rpm for 15 minutes. The plasma was separated and frozen at –80°C until assayed. Block urine samples were collected just prior to drug administration and at 12- to 24-hour intervals until 168 hours post-dose to measure renal clearance of ribavirin. Samples obtained during each collection period were refrigerated. After measuring total volume, a 25-mL aliquot from each block sample was frozen at –80°C until assayed. Plasma concentrations of ribavirin were determined using a high-performance liquid chromatography/mass spectrometric method validated with respect to linearity, precision, accuracy, limit of quantification (LOQ; 50 ng/mL), and selectivity. Urine concentrations of ribavirin were determined using a high-performance liquid chromatographic-mass spectrometric method, validated with respect to linearity, precision, accuracy, LOQ (250 ng/mL), and selectivity. In brief, solid-phase extraction was performed on samples using phenylboronic acid columns, after addition of the internal standard ($^{13}C_3$-ribavirin) and di-ammonium hydrogen orthophosphate buffer. Columns were eluted with a solution of formic acid in 50/50 methanol/water (v/v). The resulting eluate was injected into a Hewlett-Packard 1090 Series II HPLC (Palo Alto, CA, USA) with a SCIEX API 300 MS/MS detector (Framingham, MA, USA), fitted with a hypersil 3.0 × 4.6 mm analytical column (3-µm particle size). The mobile phase consisted of acetonitrile (82%) and ammonium acetate (18%). Assay precision and bias were less than 11%, respectively, for all samples.

Safety was assessed based on the results of vital signs, which were measured at screening, immediately prior to dosing (0 hour), and then at regular intervals until 168 hours post-dose. Electrocardiograms and laboratory assessments were obtained at screening and 168 hours post-dosing. Adverse events were assessed according to the Common Toxicity Criteria (CTC) grading system.

### 2.3. *Pharmacokinetic analysis*

Plasma and urine ribavirin concentrations above the LOQ (plasma 50 ng/mL; urine 250 ng/mL) were used to calculate pharmacokinetic parameters using model-independent methods (*23*). The maximum plasma concentration ($C_{max}$) and time to maximum plasma concentration ($T_{max}$) were the observed values. The area under the plasma concentration-time curve from time zero to the time of the final quantifiable sample ($AUC_{tf}$) was calculated using the linear trapezoidal method. Individual terminal rate constants could not be determined with precision, therefore the elimination half-life ($t_{½}$) and $AUC_I$ were not reported. Pharmacokinetic analysis is consequently limited to estimation of the individual $AUC_{tf}$ value instead of the $AUC_I$. Apparent plasma clearance (CL/F) was calculated by dividing dose by the $AUC_{tf}$. Clearance (CLr) was calculated by dividing the amount excreted ($A_e$) in the urine from time 0 to 168 hours by the $AUC_{tf}$.

### 2.4. *Statistical analyses*

Summary statistics were determined for the pharmacokinetic parameters of each group. Analyses of variance were used to extract group effects for AUC and $C_{max}$ in the original and log-transformed scales, and for $T_{max}$ in the original scale. All pairwise contrasts were presented without adjustment for multiple comparisons, and were based on residual errors from the analyses of variance. Linear regression analyses were performed to evaluate the association between CL/F and CLr with CLcr.

## 3. Results

### 3.1. *Patient characteristics*

Twenty-four participants were enrolled. Six subjects had

**Table 1. Demographic and baseline characteristics of 24 participants**

| | Group I (*n* = 6) | Group II (*n* = 6) | Group III (*n* = 6) | Group IV (*n* = 6) |
|---|---|---|---|---|
| Mean age, y (range) | 35.5 (21-51) | 49.3 (30-64) | 46.0 (27-64) | 39.3 (28-52) |
| Female/male (*n*) | 3/3 | 2/4 | 4/2 | 2/4 |
| Race (*n*) | | | | |
| White | 6 | 4 | 3 | 4 |
| Black | 0 | 1 | 1 | 1 |
| Hispanic | 0 | 1 | 2 | 1 |
| Mean weight, kg (range) | 77.5 (65-90) | 78.8 (70-94) | 78.7 (57-96) | 74.7 (50-94) |
| Mean height, cm (range) | 173.8 (160-186) | 172.7 (168-180) | 167.3 (157-187) | 168.8 (157-180) |

**Table 2. Ribavirin pharmacokinetic parameters after a single oral 400-mg dose in patients with varying degrees of renal insufficiency**

| Parameter, mean (%CV) | Group I (*n* = 6) | Group II (*n* = 6) | Group III (*n* = 6) | Group IV (*n* = 6) |
|---|---|---|---|---|
| CLcr (mL/min) | 142 (36) | 74 (11) | 50 (22) | 18 (21) |
| $C_{max}$ (ng/mL) | 630 (64) | 821 (48) | 732 (63) | 1,161 (29) |
| $T_{max}$ (h) | 1.5 (37) | 2.0 (55) | 1.2 (35) | 2.2 (45) |
| $AUC_{tf}$ (ng•h/mL) | 9,646 (57) | 17,451 (44) | 20,413 (54) | 31,687 (19) |
| CL/F (mL/min) | 887 (50) | 497 (71) | 403 (49) | 216 (17) |
| CLr (mL/min) | 129 (33) | 71.8 (55) | 35.8 (58) | 11.6 (31) |
| $A_e$ (0-168 h; mg) | 65.7 (40) | 61.0 (21) | 34.9 (23) | 21.3 (18) |

Data indicate mean (% coefficient of variation).
Abbreviations: AUC, area under the serum concentration-time curve from time zero to time of final quantifiable sample; $A_e$, amount excreted in urine; CL/F, total body clearance; CLr, renal clearance; CLcr, creatinine clearance; $C_{max}$, peak serum concentration; $T_{max}$, time of peak serum concentration.

normal renal function and 18 had varying degrees of renal impairment (Table 1). Data from all subjects were included in the pharmacokinetic and safety analyses.

### 3.2. *Pharmacokinetics*

Mean $T_{max}$ values were similar between all four groups, ranging between 1.2 and 2.2 hours, indicating rapid absorption of ribavirin. There were trends for higher $C_{max}$ and $AUC_{tf}$ values in groups with more severe renal dysfunction (Table 2). $AUC_{tf}$ was approximately 2-fold higher in subjects in group III, and approximately 3-fold higher in subjects in group IV, than in subjects with normal renal function (20,413 ng·hr/mL and 31,687 ng·hr/mL, respectively *vs*. 9,646 ng·hr/mL). The differences for AUC were significant in both the original and log-transformed scales ($p < 0.05$). However, there was considerable overlap between the individual $AUC_{tf}$ values among groups I-III (Figure 1). Intergroup differences in $C_{max}$ were not significant. Ribavirin concentration-time profiles are shown in Figure 2. There were prolonged terminal elimination phases in groups II-IV, with higher concentrations seen in groups with greater levels of renal dysfunction.

Both ribavirin CL/F and CLr decreased with declining renal function, with mean CL/F reduced by ~50% in group III and 75% in group IV compared with subjects with normal renal function. Regression of CL/F and CLcr showed the following statistically significant relationship: $CL/F = 153 + (4.89 \times CLcr)$ ($r^2 = 0.47$, $p < 0.05$). Regression of CLr against CLcr was also highly statistically significant ($CLr = 1.23 + (0.86 \times CLcr)$; $r^2 = 0.70$, $p < 0.001$).

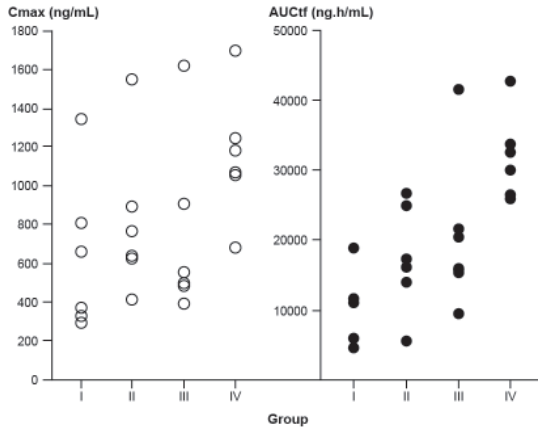


**Figure 1. Individual patient ribavirin $C_{max}$ and $AUC_{tf}$ values for groups I-IV.**

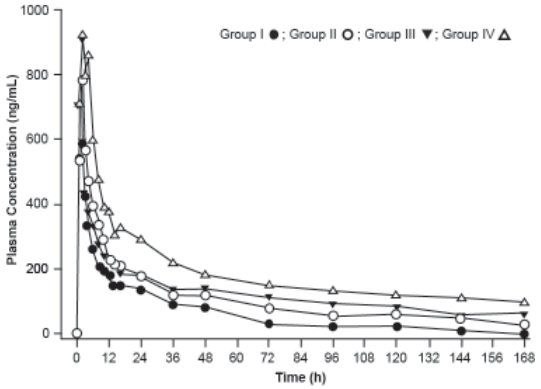


**Figure 2. Mean ribavirin concentration-time profiles following administration of a single oral 400-mg dose.** Group I (●); group II (○); group III (▼); group IV (△).

3.3. *Safety*

Ribavirin was safe and well tolerated when administered as a single oral 400-mg dose to subjects with renal impairment. Twenty-three adverse events were reported by 14 of 24 participants, the most common being headache (6 reports), nausea (3 reports), and fatigue, dizziness, and musculoskeletal pain (2 reports each). The majority of adverse events were mild and transient. Severe viral gastroenteritis and pneumonia were each reported in one patient; however, both were considered unrelated to study medication. Apart from expected laboratory test abnormalities in subjects with renal dysfunction in groups II to IV, there were no changes of clinical relevance noted during this study.

## 4. Discussion

The main finding of this study was that ribavirin exposure is significantly increased in patients with renal impairment. The safety and tolerability of a single oral dose of ribavirin were acceptable in all subjects.

Ribavirin is eliminated by both renal and hepatic routes, with gastrointestinal metabolism accounting for the majority of first-pass elimination of the parent molecule (*13,17*). Although renal excretion accounts for only 5-15% of total elimination of ribavirin (*13,18*), proportionally much greater changes in pharmacokinetic parameters were observed in patients with renal dysfunction compared with controls, and the magnitude of these changes increased with the severity of renal impairment. One possible explanation is that metabolism of ribavirin may be altered in patients with renal failure.

Although the mechanisms contributing to changes in nonrenal clearance in subjects with renal dysfunction are poorly understood, such changes are not uncommon findings with many drugs (*24,25*). Ribavirin is almost entirely absorbed after oral administration but undergoes significant first-pass metabolism, and absolute bioavailability is approximately 50% (*26*). The enzymes responsible for this process and their localization have not yet been identified; however, the site of metabolism is cytosolic and not ribosomal. Hydrolysis to form the carboxamide metabolite is one of the main metabolic pathways for ribavirin (*27*), and hydrolysis reactions are reportedly reduced in chronic renal failure (*28*).

There may be some similarities between the findings of the present study and the effect of renal impairment on didanosine pharmacokinetics (*29*). Didanosine and ribavirin are both purine nucleoside analogues, and both are substrates for the N1 nucleoside transporter. In subjects with normal function, renal clearance accounts for ~50% of didanosine's total clearance; however, in patients with end-stage renal disease, didanosine AUC was increased 4- to 5-fold (*29*). This difference was primarily due to changes in renal and nonrenal clearance estimates; it was not due to altered absolute bioavailability, and changes in volume of distribution were small (*29*). This report concluded that the pharmacokinetic changes were due to altered metabolism of didanosine associated with renal failure.

Although the present study has identified changes in ribavirin pharmacokinetics associated with reduced renal function, it has not been possible to use these data to develop dose reduction strategies for long-term use of ribavirin. The single-dose pharmacokinetics of ribavirin do not predict steady-state kinetics because of its extensive accumulation (*26*). A study in patients with chronic hepatitis C and renal impairment highlights the difficulties associated with ribavirin administration in this population (*30*). Of seven patients receiving ribavirin as a component of their antiviral medication, one had a stable ribavirin dose throughout the study, four were required to reduce their initial dose, and only two were able to increase their initial ribavirin dose. In this study, all but one patient completed treatment with ribavirin doses between 200 and 600 mg/day. In another study, Bruchfeld and colleagues examined the pharmacokinetics of ribavirin in patients undergoing treatment of HCV, either with normal renal function or with renal impairment (glomerular filtration rate (GFR) of 5-57 mL/min) (*31*). Most patients in this study were also receiving native interferon α, in line with standard HCV therapy at that time. Ribavirin pharmacokinetics were linearly dependent on renal function with a small nonrenal clearance dependent on body weight and age. Estimated GFR was a significantly better predictor of ribavirin clearance than body weight, although up to 40% of inter-individual variability in ribavirin total clearance was not explained by estimated GFR and body weight. Based on their data, the authors suggested that ribavirin dosage should be primarily based on renal function and proposed a dosing schedule based on GFR and body weight (*31*). Other groups have used pharmacokinetic monitoring of ribavirin (*32,33*), adjustment of ribavirin dose based on hemoglobin levels (*32,33*), dose titration strategies (*33,34*), or administration of erythropoietin (*34*) to titrate ribavirin levels within a therapeutic range. The prescribing information for ribavirin indicates that patients with creatinine clearance values < 50 mL/min were not included in phase 3 efficacy studies and, consequently, use of ribavirin is contraindicated in patients with CLcr < 50 mL/min (*35*). At this time it is not possible to recommend ribavirin doses for use in patients with CLcr < 50 mL/min.

Single 400-mg oral doses of ribavirin were generally safe and well tolerated in healthy volunteers with normal renal function and in patients with renal insufficiency. The most commonly reported adverse event, headache, has been reported previously following single- and multiple-dose administration of ribavirin (*14*), and no serious drug-related adverse events were reported.

In conclusion, ribavirin pharmacokinetics are substantially altered in subjects with stable chronic renal impairment compared with controls. According to prescribing information, ribavirin may be used in patients with CLcr > 50 mL/min; however, additional studies are needed to establish safe dosing regimens for patients with CLcr < 50 mL/min.

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**Conflicts of interest**

Drs. Gupta, Glue, and Kantesaria were employees of Schering Plough Corporation at the time this study was conducted. Dr. Glue is also an author on patent US6824768 B2. Dr. Gupta and Dr. Kantesaria have no other disclosures.

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