

## Exploring the influence of renal dysfunction on the pharmacokinetics of ribavirin after oral and intravenous dosing

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### Summary

Although ribavirin is minimally cleared by renal elimination, its pharmacokinetics are substantially altered in patients with chronic renal impairment. This open-label study assessed the pharmacokinetics of single 400-mg oral and intravenous (IV) doses of ribavirin in two healthy volunteers and 12 patients with varying degrees of chronic renal impairment. Blood and urine samples were collected pre-dose and up to 168 h post-dose for pharmacokinetic analyses. Ribavirin area under the plasma concentration-time curve from time zero to time of final quantifiable sample and maximum plasma concentration values were increased, and total plasma clearance (CL), renal clearance (CL<sub>r</sub>), non-renal clearance (CL<sub>nr</sub>), volume of distribution at steady state (Vd<sub>ss</sub>), and amount excreted values were reduced in patients with renal dysfunction compared with those who had normal renal function. Following IV administration, mean CL<sub>r</sub> was 54%, 23%, and 10% in patients with mild, moderate, and severe renal dysfunction, respectively, relative to control subjects, and was 56%, 28%, and 9% of control values after oral dosing. After IV dosing, mean CL<sub>nr</sub> was 94%, 76%, and 75% of control values in patients with mild, moderate, and severe renal dysfunction, respectively, and was 54%, 48%, and 27% of control values after oral dosing. Mean oral bioavailability of ribavirin was 35%, 60%, 57%, and 71% in control subjects and patients with mild, moderate, and severe renal dysfunction, respectively. These data indicate that there are multiple mechanisms (increased oral bioavailability, reduced CL<sub>r</sub> and CL<sub>nr</sub>, reduced Vd) contributing to altered ribavirin pharmacokinetics in chronic renal impairment.

**Keywords:** Intravenous, oral, pharmacokinetics, ribavirin, renal dysfunction, creatinine clearance, bioavailability, excretion

### 1. Introduction

Ribavirin is a broad-spectrum antiviral agent that is active against a number of viruses, including hepatitis C virus (HCV) (1-6). In combination with pegylated interferon, ribavirin is an established treatment for chronic HCV infection (7,8), and more recently has also become a component of protease inhibitor-based triple therapy regimens with boceprevir or telaprevir (9-12).

Ribavirin is contraindicated in patients with creatinine clearance < 50 mL/min (13). Pharmacokinetic studies

in healthy volunteers and patients with HCV infection indicate that although both renal and hepatic pathways contribute to ribavirin elimination, the relative contribution of renal pathways is comparatively low, accounting for only 5-15% of the total elimination (14-19). It is therefore somewhat surprising that ribavirin has been shown to accumulate in patients with renal failure (20,21). A recent pharmacokinetic study of single-dose oral ribavirin in patients with renal dysfunction highlighted substantial alterations in ribavirin pharmacokinetics associated with declining renal function (22). The authors proposed that changes in ribavirin metabolism associated with renal impairment might underlie the altered pharmacokinetics seen in this patient group. The objective of the present study was to compare ribavirin pharmacokinetics after single oral and intravenous (IV) doses in patients with renal dysfunction, to further evaluate mechanisms contributing to the altered pharmacokinetics.

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## 2. Materials and Methods

This was an open-label, parallel-group, single-dose, and 2-stage study. The first stage was designed to assess the pharmacokinetic properties of a single oral 400-mg dose of ribavirin, whereas the second stage assessed the pharmacokinetics of a single 400-mg IV dose, in subjects with varying degrees of stable chronic renal insufficiency. Subjects who had received oral ribavirin during the first stage of the study and who continued to meet the enrollment criteria were permitted to enroll in the second phase of the study. The two stages of the study were separated by a washout period of several months. The study was conducted in accordance with the 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, Austin, Texas.

### 2.1. Study population

Male and female subjects, 18 to 65 years of age, who had normal renal function or varying degrees of stable chronic renal insufficiency were enrolled. Subjects with normal renal function (creatinine clearance [ $CL_{cr}$ ] > 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 ( $CL_{cr}$  < 90 mL/min) were excluded if they had significant medical disorders unrelated to their renal disorder that would substantially interfere with their ability to participate in the study.

### 2.2. Study design

During stage 1, participants fasted overnight and then received a single oral 400-mg dose of ribavirin (2 × 200-mg capsules) with 200 mL water. For analysis, participants were divided into 4 groups according to  $CL_{cr}$  (based on a 24-h urinary collection): group I,  $CL_{cr}$  > 90 mL/min/1.73 m<sup>2</sup> (normal); group II,  $CL_{cr}$  > 61 and ≤ 90 mL/min/1.73 m<sup>2</sup> (mild renal dysfunction); group III,  $CL_{cr}$  ≥ 31 and ≤ 60 mL/min/1.73 m<sup>2</sup> (moderate renal dysfunction); and group IV,  $CL_{cr}$  10-30 mL/min/1.73 m<sup>2</sup> (severe renal dysfunction). During stage 2, participants again fasted overnight and then received a single IV 400-mg dose of ribavirin solution (13.3 mL of 30 mg/mL solution), infused over 15 min (0.89 mL/min) using a syringe pump. For analysis, participants were again divided into groups I to IV as described for stage 1. Participants continued fasting until 4 hours after the dose and were discharged from the study center after 48

h. Subsequent samples were collected on an outpatient basis.

### 2.3. Sample collection and assay for pharmacokinetic assessments

After oral dosing, blood samples for determination of plasma ribavirin concentrations were obtained immediately prior to drug administration and then at specified time intervals until 168 h after the dose. After IV infusion dosing, additional blood samples were collected at 0.08, 0.16, 0.25, and 0.5 h after the dose and then again at the same time intervals as for the oral dose until 168 h after the dose. After collection, the plasma was separated from blood samples and frozen at -80°C until analysis.

Block urine samples were collected immediately prior to drug administration and at 12- to 24-h intervals until 168 h following the dose. Plasma and urine concentrations of ribavirin were determined using high-performance liquid chromatography/tandem mass spectrometry, as previously described (22).

### 2.4. Pharmacokinetic analysis

Plasma and urine ribavirin concentrations above the limit of quantitation (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 ( $t_{1/2}$ ) and area under the plasma concentration-time curve from time zero to infinity ( $AUC_{\infty}$ ) were not reported. Pharmacokinetic analysis was consequently limited to estimation of individual  $AUC_{tf}$  value instead of  $AUC_{\infty}$ . Total plasma clearance (CL) was calculated by dividing the dose by  $AUC_{tf}$  after IV dosing. Renal clearance ( $CL_r$ ) was calculated by dividing the amount excreted ( $A_e$ ) in the urine from time 0 to 168 h by the  $AUC_{tf}$ . Nonrenal clearance ( $CL_{nr}$ ) was the difference between CL and  $CL_r$ .

Absolute bioavailability (F) was calculated (as percentage) for each subject as [ $AUC^{PO}(tf, po) \times dose^{IV}$ ] / [ $AUC^{IV}(tf, po) \times dose^{PO}$ ], where *tf*, *po* was the *tf* for that subject following oral administration, and  $AUC^{PO}(tf, po)$  and  $AUC^{IV}(tf, po)$  were AUC values from time zero to *tf*, for *po* dose following administration of oral and IV doses to the same subjects, respectively. Absolute bioavailability (F) was expressed as a percentage and was not calculated from urine data, because most subjects had renal impairment and could not provide adequate urine samples.

The volume of distribution at steady state ( $V_{d_{ss}}$ ) was calculated using the following equation:  $(CL) \times MRT_{tf} - CL \times 1/2$  (infusion duration), where  $MRT_{tf}$  was the mean residence time obtained from the ratio of area under the first moment curve from time zero to  $t_f$  ( $AUMC_{tf}$ ) and  $AUC_{tf}$ .  $CL_r$  was calculated by dividing  $A_e$  in urine over 168 h after IV dosing by  $AUC_{tf}$ .

### 2.5. Safety

Safety was assessed based on the results of vital signs, which were measured at screening, immediately prior to dosing (0 h), and then at regular intervals until 168 h following the dose. Electrocardiograms and laboratory assessments were obtained at screening and 168 h after dosing. The intensity (severity) of adverse events was assessed according to the Common Toxicity Criteria (CTC) grading system where applicable, or graded as mild, moderate, severe, or life threatening as defined in the protocol.

### 2.6 Statistical analyses

Summary statistics were determined for the pharmaco-

kinetic parameters of each group. Linear regression analyses were used to determine the relationship between  $CL_{cr}$  and  $CL_r$ ,  $V_{d_{ss}}$ , and F.

## 3. Results

### 3.1. Patient characteristics

All 14 subjects enrolled received single oral and IV doses of ribavirin (Table 1). Data from all subjects were included in the pharmacokinetic analyses and in evaluations of safety and tolerability.

### 3.2. Pharmacokinetic assessment

After a single oral dose of ribavirin, mean  $AUC_{tf}$  increased with the severity of renal dysfunction; however, there was no notable change in  $C_{max}$  associated with declining renal function (Table 2). After a single IV dose of ribavirin, mean  $C_{max}$  values (at end of ribavirin infusion) were similar in groups I, II, and IV, and slightly higher in group III. In contrast, renal dysfunction was associated with a corresponding increase in mean  $AUC_{tf}$  of 1.3-, 2.0-, and 2.0-fold in

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

	Group I (n = 2)	Group II (n = 5)	Group III (n = 3)	Group IV (n = 4)
Mean age, y (range)	43 (34-52)	52 (30-64)	48 (27-64)	40 (30-50)
Women/men (n)	2/0	1/4	2/1	2/2
Race (n)				
White	2	3	2	2
Black	0	1	0	1
Hispanic	0	1	1	1
Mean weight, kg (range)	83.5 (74-93)	81.6 (71-92)	68.7 (55-93)	77.3 (47-103)
Mean height, cm (range)	164.5 (160-169)	173.6 (168-180)	169.3 (158-187)	166.8 (157-173)
CL <sub>cr</sub> (mL/min [%CV])	114 (-)	74 (13)	44 (23)	19 (22)

CL<sub>cr</sub>, creatinine clearance; %CV, % coefficient of variation.

**Table 2. Mean (%CV) pharmacokinetic parameters of ribavirin after single oral and IV 400-mg doses in patients with varying degrees of renal insufficiency**

	Group I (n = 2) CL <sub>cr</sub> > 90 mL/min		Group II (n = 5) CL <sub>cr</sub> 61-90 mL/min		Group III (n = 3) CL <sub>cr</sub> 31-60 mL/min		Group IV (n = 4) CL <sub>cr</sub> 10-30 mL/min	
	Oral	IV	Oral	IV	Oral	IV	Oral	IV
CL <sub>cr</sub> (mL/min)	114 <sup>a</sup>		74 (13)		44 (23)		19 (22)	
C <sub>max</sub> (ng/mL)	339 <sup>a</sup>	12,044 <sup>a</sup>	829 (53)	13,043 (17)	994 (57)	16,305 (45)	1,274 (24)	1,0791 (37)
AUC <sub>tf</sub> (ng•h/mL)	5,555 <sup>a</sup>	22,924 <sup>a</sup>	15,610 (44)	29,341 (20)	25,857 (52)	46,882 (42)	32,574 (21)	47,442 (31)
CL (mL/min)	-	296 <sup>a</sup>	-	236 (23)	-	168 (55)	-	151 (30)
CL <sub>r</sub> (mL/min)	147.6 <sup>a</sup>	107 <sup>a</sup>	76.8 (55)	58.1 (36)	26.5 (33)	24.6 (41)	11.8 (30)	10.2 (42)
CL <sub>nr</sub> (mL/min)	-	189 <sup>a</sup>	-	178 (25)	-	143 (59)	-	141 (30)
V <sub>d<sub>ss</sub></sub> (L)	-	639 <sup>a</sup>	-	634 (15)	-	506 (42)	-	469 (25)
A <sub>e</sub> (mg)	49.1 <sup>a</sup>	145 <sup>a</sup>	58.2 (20)	98.6 (31)	36.5 (18)	62.7 (39)	21.9 (21)	26.5 (24)
% Dose	12 <sup>a</sup>	36 <sup>a</sup>	15 (20)	25 (31)	4 (13)	15.7 (39)	5 (8)	6.6 (24)
%F	35 <sup>a</sup>	-	60 (35)	-	57 (30)	-	71 (20)	-

AUC<sub>tf</sub>, area under the serum concentration-time curve from time zero to time of final quantifiable sample; A<sub>e</sub>, amount excreted in urine; CL, total plasma clearance; CL<sub>r</sub>, renal clearance; CL<sub>cr</sub>, creatinine clearance; CL<sub>nr</sub>, non-renal clearance; C<sub>max</sub>, maximum plasma concentration; IV, intravenous; V<sub>d<sub>ss</sub></sub>, volume of distribution at steady state; F, absolute bioavailability. <sup>a</sup>%CV not determined when n < 3.

groups II, III, and IV, respectively, compared with the mean  $AUC_{cr}$  in subjects with normal renal function.

In patients receiving IV ribavirin, mean CL decreased as  $CL_{cr}$  declined (mean CL relative to controls was 80%, 57%, and 51% in groups II, III, and IV, respectively). Regression of CL against  $CL_{cr}$  was highly statistically significant ( $CL = 102 + 1.81 \times CL_{cr}$ ;  $r^2 = 0.64$ ,  $p < 0.001$ ).

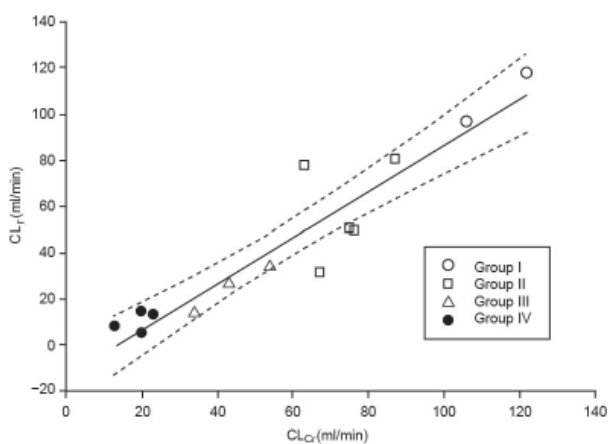
In subjects with normal renal function receiving IV ribavirin, mean ribavirin  $CL_r$  was ~36% of CL (107 mL/min vs. 296 mL/min). Ribavirin  $CL_r$  declined with decreasing renal function (Figure 1). Regression of  $CL_r$  against  $CL_{cr}$  was highly statistically significant ( $CL_r = -13.1 + 0.99 \times CL_{cr}$ ;  $r^2 = 0.88$ ,  $p < 0.001$ ). Ribavirin  $CL_{nr}$  also tended to decline with decreased renal function. Compared with control subjects with normal renal function, the degree of decline in mean  $CL_r$  was greater in groups II, III, and IV (54%, 23%, and 10%, respectively) than that in mean  $CL_{nr}$  (94%, 76%, and 75%).

Following IV administration, ribavirin  $Vd_{ss}$  also declined with decreasing renal function. Regression of  $Vd_{ss}$  against  $CL_{cr}$  was statistically significant ( $Vd_{ss} = 414 + 2.55 \times CL_{cr}$ ;  $r^2 = 0.38$ ,  $p < 0.02$ ).

Absolute bioavailability following oral administration was 35%, 60%, 57%, and 71% for groups I–IV, respectively. Although absolute bioavailability tended to increase with renal dysfunction, regression of bioavailability (%F) against  $CL_{cr}$  was not statistically significant ( $p = 0.12$ ).

### 3.3. Safety

Ribavirin was safe and well tolerated when administered as a single oral or IV dose of 400 mg to subjects with renal dysfunction. Eight adverse events of mild to moderate intensity were reported, the most common being headache ( $n = 3$ ), with individual reports of allergy, hyperglycemia, hypoglycemia,



**Figure 1. Relationship between individual renal clearance ( $CL_r$ ) of intravenous ribavirin and creatinine clearance ( $CL_{cr}$ ) in subjects in groups I to IV.** The dotted lines represent the upper and lower bounds of 95% confidence intervals.

pharyngitis, and thrombocytopenia. Apart from the expected laboratory test abnormalities in subjects with renal dysfunction, there were no changes of clinical relevance noted during this study.

## 4. Discussion

Ribavirin is eliminated by both renal and hepatic routes, with gastrointestinal metabolism accounting for the majority of first-pass elimination of the parent molecule (24). Although renal excretion accounts for only 5-15% of the total elimination (24), the results of the present study show that the pharmacokinetic properties of ribavirin are significantly altered in subjects with renal dysfunction compared with subjects with normal renal function. We found that ribavirin AUC and  $C_{max}$  values were increased, and CL,  $CL_r$ ,  $CL_{nr}$ ,  $Vd_{ss}$ , and  $A_e$  values were reduced in subjects with renal dysfunction compared with controls with normal renal function. The magnitude of these changes increased with the severity of renal dysfunction. We have identified 4 possible mechanisms for the altered pharmacokinetics of ribavirin in subjects with renal dysfunction; these are discussed in the text that follows.

### *Reduction of renal clearance in absolute and proportional terms*

In the present study, mean  $CL_r$  after IV dosing in control subjects was 36%, which is similar to previously reported results (16). Mean  $CL_r$  was 54%, 23%, and 10% relative to subjects with normal renal function in groups II, III, and IV, respectively. In these subjects, the proportion of total CL accounted for by  $CL_r$  after IV dosing declined as renal function decreased (25%, 15%, and 7%, in groups II, III, and IV, respectively).

Mean  $CL_r$  after oral dosing was 56%, 28%, and 9% compared with controls in groups II, III, and IV, respectively; these values are very similar to those observed after IV dosing. In contrast, in these subjects, the proportion of total CL accounted for by  $CL_r$  after oral dosing declined as renal function decreased (14%, 9%, and 5% in groups II, III, and IV, respectively).

Thus,  $CL_r$  as a proportion of total CL was always greater after IV dosing compared with oral dosing, both in controls and in subjects with renal dysfunction. This could reflect a reduction in first-pass metabolism, which is substantial after oral dosing (~50%) (24). Also, the ratio of oral  $CL_r$ :IV  $CL_r$  was smallest for subjects with normal renal function (0.42) and was progressively greater as renal function declined (0.56, 0.60, and 0.71 for groups II, III, and IV, respectively). One interpretation of this finding is that the proportion of ribavirin cleared by first-pass metabolism decreases as renal function declines. This would be consistent with the finding that  $CL_{nr}$  was reduced and F increased as renal function declined (as follows).

### *Reduced non-renal clearance in absolute terms*

In addition to changes in  $CL_r$ ,  $CL_{nr}$  also decreased as renal function declined. Compared with controls, mean  $CL_{nr}$  was 94%, 76%, and 75% in groups II, III, and IV, respectively, after IV dosing. After oral dosing, mean  $CL_{nr}$  relative to controls was 54%, 48%, and 27% in groups II, III, and IV, respectively. In a separate study in patients with hepatic dysfunction, there were no changes in single-dose pharmacokinetic parameters in patients with hepatic dysfunction compared with controls (17). Thus, the changes in  $CL_{nr}$  in the present study may indicate a significant effect of renal dysfunction on nonhepatic sites of ribavirin metabolism. Although the mechanisms underlying changes in nonrenal clearance in subjects with renal dysfunction are poorly understood, this is a common finding with many drugs (25,26).

### *Increased absolute bioavailability*

A third possible mechanism is that the higher exposures noted in patients with renal dysfunction could be due to increased absolute bioavailability (F). The present study showed that  $CL_r$  as a proportion of total CL was always higher after IV dosing compared with oral dosing, both in control subjects and in patients with renal dysfunction, reflecting the absence of a first-pass metabolism. As previously mentioned, the ratio of oral  $CL_r$  to IV  $CL_r$  was lowest for subjects with normal renal function and became progressively greater as renal function declined, which may be evidence that the proportion of ribavirin being cleared by first-pass metabolism decreased as renal function declined. This would also be consistent with the reduction in  $CL_{nr}$  described earlier. Ribavirin is almost entirely absorbed after oral administration, but undergoes significant first-pass metabolism, and absolute bioavailability is ~50% (24). 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). Increased absolute bioavailability has been reported in patients with renal dysfunction for a number of other drugs (26,29-31), including metoclopramide, erythromycin, propranolol, and other  $\beta$ -blockers.

### *Reduced volume of distribution*

A fourth possible mechanism is that ribavirin Vd is affected by renal dysfunction. In the present study, ribavirin  $Vd_{ss}$  declined with decreasing renal function after IV administration, and regression of  $Vd_{ss}$  against  $CL_{cr}$  was statistically significant. Elimination-phase

profiles and  $t_{1/2}$  values after oral administration were similar in patients with declining renal function (in groups II, III, and IV); however, the Vd after oral administration was not determined.

Notable similarities exist between the findings of the present study and the impact of renal impairment on the pharmacokinetics of another purine nucleoside analogue, didanosine (32). Both didanosine and ribavirin are substrates for the N1 nucleoside transporter. Renal clearance accounts for ~50% of the total clearance of didanosine in subjects with normal renal function; however, didanosine AUC was increased 4- to 5-fold in patients with end-stage renal disease (32). Renal impairment was associated with reductions in didanosine  $CL_r$ ,  $CL_{nr}$ , and Vd, but had no effect on absolute bioavailability (32). The authors concluded that the changes in didanosine pharmacokinetics observed in patients with renal impairment may be due to altered metabolism of didanosine associated with renal failure.

In the present study, single 400-mg oral and IV 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 (15), and no serious drug-related adverse events were reported.

A possible shortcoming of this study should be acknowledged. Although a relatively small numbers of subjects were enrolled, the pharmacokinetic parameters for each group were similar to those previously reported (21,22), and in many analyses renal function was evaluated as a continuous variable.

The present study has identified a number of possible mechanisms (changes in  $CL_r$  and  $CL_{nr}$ , increased bioavailability, and altered Vd) that might account for the altered single-dose pharmacokinetic profile of ribavirin in patients with renal dysfunction. As ribavirin has a well-established exposure-toxicity profile, it is important to ensure that patients with renal dysfunction are dosed appropriately to avoid excessive hemolysis. Because of the extensive accumulation that occurs with multiple-dose ribavirin pharmacokinetics, this single-dose study cannot provide definitive dosing guidelines for patients with renal impairment (15,24). Furthermore, patients with chronic renal dysfunction also appear more likely to develop ribavirin-induced anemia than do control subjects. In addition to ribavirin-induced hemolysis, other factors that may affect ribavirin dosing include inadequate marrow responsiveness to anemia as well as reduced erythrocyte longevity due to uremia.

In conclusion, this study has identified a number of mechanisms to explain the alterations in ribavirin pharmacokinetics in subjects with stable chronic renal impairment, generally similar to those reported previously for didanosine.

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