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Ribavirin Levels in Post Liver Transplant Patients Treated for Recurrent Hepatitis C Viral Infection

A. Jain, R. Vekatramanan, B. Yelochan, R. Kashyap, A. Marcos, and J. Fung

ABSTRACT

Hepatitis C virus (HCV) infection is the most common indication for liver transplantation (LTx) in the United States. Ribavirin with pegylated interferon is the only treatment option for HCV recurrence in post-LTx patients. In clinical practice, for more than 50% of patients, ribavirin dose needs to be modified.

Aim. The aim of this study was to examine the role of ribavirin level and its relevance in the management of post-LTx patients in terms of renal dysfunction, efficacy, toxicity, and potential drug interactions.

Patients and methods. Thirty-four blood samples were available from 22 post-LTx patients. Ribavirin concentrations in plasma (all samples) and whole blood concentrations (16 samples) were examined. The dose of ribavirin ranged from 400 mg/d to 1000 mg/d, but concentrations were normalized to 800 mg/d.

Results. There was a wide variation in plasma concentration of ribavirin, ranging from 1.8 to 122.1 mg/mL. The concentrations were similar in whole blood and plasma. Dose-normalized concentration with creatinine clearance below 70 mL/min were significantly higher when compared with creatinine clearance above 70 mL/min ($P = .015$). Eleven patients required erythropoietin; their mean ribavirin dosage was higher but mean ribavirin concentration was lower compared to the 11 patients who did not require erythropoietin factor. There was no difference in mean ribavirin concentration in patients who cleared the virus ($n = 7$) compared and who did not clear the virus ($n = 9$). Three patients were on nucleoside reverse transcriptase inhibitors (NRTI) had significantly higher concentration (mean 87.1 μg/mL) compared to those who did not receive NRTI (mean 34.4 μg/mL, $P = .00$)

Conclusion. Ribavirin concentration in plasma and whole blood were similar, with a wide variation. Patients with impaired renal function and those who were on NRTI had significantly higher concentrations of ribavirin. The ribavirin concentrations did not predict either the clearance of HCV RNA or the need for erythropoitin factor.

HEPATITIS C viral infection (HCV) is the most common indication for liver transplantation (LTx) in the Western world.[1] Unfortunately disease recurrence is almost universal after successful LTx.[2,3] Ribavirin with pegylated interferon demonstrated improved antiviral activity.[4,5] The main side effect of ribavirin is hemolysis and in many of the prospective trials, for more than 50% of patients the drug had to be discontinued for its side effects.[6–9] Because ribavirin is cleared by kidney, dose modification with renal dysfunction has been recommended.[10,11]

The aim of the present study is to examine the role of ribavirin level and its relevance in the management of

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Table 1. Patients Characteristics

Sample no.	Subject no.	Gender	Age (y)	Ribavirin dose (mg/d)	Days on Riobavirin	Trough/ Peak Levels	Ribavirin Plasma Level	Normalized Level to Ribavirin Dose 800 mg/d	Ribavirin Whole Blood* Level	Ribavirin Whole Blood* Level Normalized to 800 mg/d	Starting Hct	Serum Creatinine (mg/dL)	Creatinine Clearance (mL/min)	HCV RNA Clearance	Need for Epogen	HAART	Proton Pump Inhibiter
1	1	m	46	1000	281	t	34.8	27.8				1.1	88.8	y			
2	2	m	61	400	360	t	45.8	91.6			34.2	1.5	47.3	no			y
3	3a				98	t	122.1	97.7			36.0	1.0	77.0				
4	3b	f	49	800	196	t	116.6	93.3				1.1	138.7	y		Nelfinavi Stavudine, Lamlvudine	y
5	4a				49	p	4.3	3.4			36.4	1.5	80.4				
6	4c	m	50	1000	105	p	45.0	36.0	38.4	30.7		1.5	80.5	no	y		y
7	4d				126	p	46.2	37.0	39.3	31.4		1.3	92.3				
8	4e				140	p	50.9	40.7				1.4	85.8				
9	5a			600	52	p	5.4	7.2			43.6	0.9	101.5				
10	5b	m	36		59	p	9.1	12.1				0.9	101.5	no	y		y
11	5d			400	143	t	60.0	120.0				0.8	104.0				
12	6	m	52	400	864	p	1.8	3.6			34.9	1.0	80.0	y			
13	7a			800	192	t	5.1	5.1			39.7	1.0	104.0				
14	7b	m	51		234	p	46.0	36.8	32.3	32.3		1.1	98.4	y	y		y
15	7c			1000	262	t	44.7	35.8	48.2	38.6		0.9	120.2				
16	12	m	61	400	80	t	31.1	62.2			39.0	1.5	50.2	no			
17	13a	m	41	800	25	t	55.8	55.8			38.3	1.0	121.0	no			y
18	13b				60	t	35.9	35.9	51.2	51.2		1.0	125.3				
19	14a	m	50	1000	304	t	13.2	10.6			31.5	0.8	121.8	no	y		
20	14b				332	t	10.7	8.6	16.9	13.5		0.9	108.3				
21	15	m	49	800	398	t	54.4	54.4			47.0	1.0	106.6	yes			
22	16	m	48	1000	206	t	83.5	66.8	63.9	51.1	43.2	1.0	107.5	no			
23	17	m	42	800	108	t	26.8	26.8	17.4	13.9	29.8	0.5	178.2	no	y	Nelfinavir, Zidovudin, Lamivudine	y
24	18	m	54	400	313	p	15.1	30.2	12.4	24.8	37.2	1.3	84.3	y			
25	19	m	58	400	2296	t	72.9	145.8	49.9	99.8	31.8	1.0	72.9	no	y		
26	20	*f*	56	800	139	p	22.6	22.6	19.7	19.7	42.8	0.8	73.5	yes			
27	21a	m	50	800	182	t	69.4	69.4	57.9	57.9	53.4	1.3	57.6	na	y	Amprinavir, Zidovudin, Lamivudine	y
28	21b				192	t	100.4	100.4				1.5	49.9				
29	22a	m	52	800	7	t	13.3	13.3			44.8	1.1	81.2	na	y		y
30	22b				14	t	25.4	25.4				1.2	74.5				
31	23	m	45	800	24	t	20.1	20.1	19.7	19.7	42.3	0.9	119.6	na			
32	24	m	52	1000	1594	t	38.4	30.7	37.8	30.2	42.0	0.9	98.1	na	y		
33	25	m	54	800	309	t	76.2	76.2	68.5	68.5	29.9	0.8	86.9	na	y		

Table 1. Continued

Sample no.	Subject no.	Gender	Age (y)	Ribavirin dose (mg/d)	Days on Riobavirin	Trough/ Peak Levels	Ribavirin Plasma Level	Normalized Level to Ribavirin Dose 800 mg/d	Ribavirin Whole Blood* Level	Ribavirin Whole Blood* Level Normalized to 800 mg/d	Starting Hct	Serum Creatinine (mg/dL)	Creatinine Clearance (mL/min)	HCV RNA Clearance	Need for Epogen	HAART	Proton Pump Inhibiter
34	26	*f*	60	400	2963	t	30.9	60.0	26.2	52.4	40.4	1.0	64.2	na	y		
Mean			50.2	736.4	294.8		41.5	44.6	36.4	36.8	39.3	1.1	94.7				
SD			6.3	234.1	471.2		31.8	36.7	16.8	22.6	5.9	0.3	27.6				
Median			50.5	800.0	187.0		37.2	36.0	38.1	31.9	39.0	1.0	90.5				

HAART, highly active antiretroviral therapy; y, yes; na, not available; m, male; f, female; p, peak; t, trough.

post-LTx patients in terms of renal dysfunction, toxicity, efficacy, and drug interaction.

PATIENTS AND METHODS

Twenty-two post-LTx patients (men 19, women 3, mean age 50.2 ± 6.3 years, range 36 to 61, median 50.5) who were on both tacrolimus and ribavirin were included in the prospective study on an IRB-approved protocol. Blood samples that had been drawn to measure tacrolimus or cyclosporine levels were retrieved and coded without patient identity to measure the concentration of ribavirin. Thirty-four blood samples from 22 individuals were available for study. Five patients had two samples each, two patients had three samples each, and one patient had four samples. Twenty-four samples were taken 10 to 12 hours after the last dose of ribavirin (trough samples) and 10 samples were taken 1 to 3 hours after morning dose of ribavirin (peak samples). The plasma concentration of ribavirin was estimated in all 34 samples and in 16 samples whole blood concentration of ribavirin was measured by high-performance liquid chromatography (HPLC). Ribavirin was measured in plasma according to the methods of Granich et al,[12] with minor modifications. Ribavirin in whole blood was measured after treatment of blood samples with 2.3 mol perchrloric acid and neutralizing the supernatant with 10 mol KOH and 0.9 mL of 250 mmol ammonium acetate and processing the supernatant the same way as plasma. Prospectively collected clinical data included on ribavirin dose, duration of ribavirin treatment, biochemical profile of liver and renal function, sequential HCV viral load, response rate, and coadministered medications. Differences between trough and peak levels, plasma concentration, and whole-blood concentration were examined. Also, the relationship of duration on ribavirin treatment, dose of ribavirin, renal function (calculated serum creatinine by Cockcroft-Gault formula[13]), need for erythropoietin to control hemolysis, coadministered medications and HCV response rate (based on sequential estimation of HCV RNA load) were examined. Because patients received different doses at the time of study, the analysis was performed with concentration normalized to daily ribavirin dose of 800 mg/d.

Statistical Analysis

Values are given as mean and standard deviation. Parametric values are compared with Pearson chi-square and means compared using independent two-tailed *t*-test. SPSS 12.0 for Windows, statistical package, was used for analysis.

RESULTS

There was a wide variation in ribavirin plasma concentration ranging from 1.8 to 122.1 μg/mL. The mean overall concentration was 42.1 + 31.5 μg/mL (median 37.2). Mean ribavirin trough concentrations were 49.4 + 32.8 μg/mL (median 41.6, range 5.1 to 122), and the mean (1 to 3 hours) peak concentration were 24.6 + 20.2 μg/mL (median 18.9, range 1.8 to 50.9; Table 1). The mean whole blood ribavirin concentration (n = 16) was 37.5 + 17.3 μg/mL (median 37.8, range 12.4 to 68.5) and mean plasma concentration of same samples was 42.7 + 21.8 μg/mL (median 42.7, range 15.1 to 76.2; Fig 1).

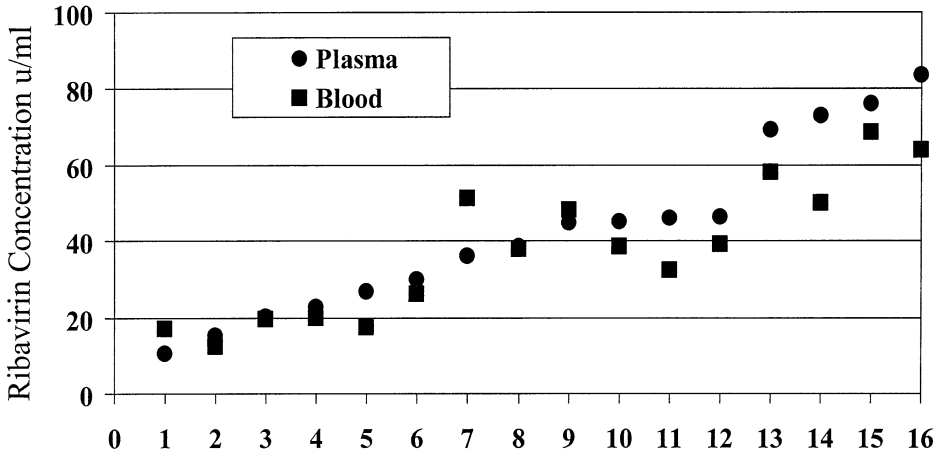

Fig 1. Plasma and whole blood concentration of Ribavirin μg/mL (n = 16).

Ribavirin Plasma Concentration and Ribavirin Dose Per Day

The dosage of ribavirin during the study period was 400 mg/d (n = 7 observations), 600 mg/d (n = 2 observations), 800 mg/d (n = 15 observations), and 1000 mg/d (n = 10 observations). The mean concentration of ribavirin for the dosage of 400 mg/d, 600 mg/d, 800 mg/d, and 1000 mg/d were 31.3 ± 43.6 (median 5.4, range 5.1 to 122.1), 20.1 ± 15.6 (median 20.1, range 9.1 to 31.1), 42.8 ± 22.3, (median 45, range 10.7 to 83.5), and 53.1 ± 35 (median 44.7, range 13.3 to 116.6), respectively. The mean Ribavirin concentration to normalized dose of 800 mg/d were 49.5 ± 21.8 μg/mL (Table 2).

Ribavirin Concentration and Renal Function

Observations were divided on the basis of calculated creatinine clearance below 70 mL/min (n = 5), above 70 and below 100 mL/min (n = 15), and more than 100 mL/min (n = 14) and correlated with ribavirin concentration. The mean ribavirin levels were lower with rising creatinine clearance despite higher doses of ribavirin. When creatinine clearance was below 70 mL/min, the mean ribavirin level was 55.3 ± 29.8 μg/mL (mean ribavirin dose was 560 mg/d). When creatinine clearance was above 70 and below 100, the ribavirin level was 41 ± 31.6 μg/mL (mean ribavirin dose 800 ± 226 mg/d). When creatinine clearance was above 100 mL/min, the ribavirin level was 38.7 ± 33 μg/mL (mean ribavirin dose 800 ± 175 mg/d (Table 2). The dose normalized concentration of ribavirin were significantly higher when creatinine clearance, was below 70 when compared with creatinine clearance above 70 but below 100 (P = .015) and above 100 mL/min (P = .015) (Fig 2A).

Need for Erythropoietin Factor (Epogen)

Erythropoietin was used when the hematocrit dropped by more than 25% or the actual value was less than 25%. Eleven patients required Epogen. Their mean starting hematocrit was 36 ± 5.4% (median 35.9, range 29 to 44.8), mean creatinine clearance was 96.7 ± 29.2 mL/min (median 98.3, range 49.9 to 178.2) and mean ribavirin dose was 820 ± 194 mg/d (range 400 to 1000) and mean ribavirin concentration was 36.0 ± 26.7 μg/mL (median 34.2, range 43.5 to 110.4). For the 11 patients who did not require Epogen, mean creatinine clearance was 89.7 ± 26.6 mL/min (median 86.6, range 47.3 to 125.3), starting hematocrit 38.9 + 4.8% (median 28.3, range 31.8 to 243.2), mean Ribavirin dose 685 ± 232 mg/d and ribavirin concentration of 50.9 ± 36.5 μg/mL (median 40.9; range 18 to 126.1). Ribavirin dose normalized concentration was 61.2 ± 44.0 μg/mL when erythropoietin factor was used and 48.4 ± 30.2 μg/mL when erythropoietin factor was not used (table 2; P = .20) (Fig 2C).

Response Rates During the Study Period

Sixteen patients had sequential HCV RNA viral load available before and after pegintron and ribavirin treatment. Seven patients cleared and nine patients did not clear the virus. Among patients who cleared the virus, the mean ribavirin levels were 42.2 ± 40.3 μg/mL (median 31.1, range 1.8 to 116). For patients who did not clear the virus, mean ribavirin levels were 52.2 ± 29.8 μg/mL (median 42, range 13.2 to 100.4). The dose-normalized mean ribavirin level was 39.0 ± 30.0 μg/mL when HCV RNA was cleared and 68.9 ± 43.6 μg/mL when HCV RNA was not cleared (P = .30; Table 2) (Fig 2B).

Effect of Coadministered Drug

Five samples from three patients were examined when patients where on highly active antiretroviral therapy (HAART) containing nucleoside reverse transcriptase inhibiter (NRTI). The mean ribavirin concentrations were 87.3 ± 39.4 μg/mL, compared to remaining 29 samples where mean ribavirin concentrations were 34.4 ± 22.9 μg/mL (P = .00). This was also significant when normalized ribavirin concentration were compared (Table 2) (Fig 2D).

Table 2. Ribavirin Dose (mg/d) and Levels (μg/mL)

	Samples (*n*)	Subjects (*n*)	Mean Ribavirin Dose (mg/d)	Ribavirin Levels (μg/mL)				Normalized Ribavirin Levels (ng/mL) to Ribavirin 800 mg/d				*P* Value[#]
				Mean	SD	Median	Range	Mean	SD	Median	Range	
Plasma	34	22	775	49.6	31.8	37.1	1.8–122.1	44.6	36.7	36.0	3.4–145.8	
Trough	24	18	767 ± 210	49.4	32.8	41.4	5.1–122.1	49.1	33.5	41.6	5.1–145.8	
Peak	10	4	760 ± 245	24.6	20.2	18.9	1.8–46.0	23.0	15.1	26.4	3.4–40.7	
Whole blood*	16	14	878 ± 205	36.1	16.8	38.1	12.4–68.5	36.78	22.792	31.87	13.5–99.8	
Ribavirin dose (mg/d)												
400	7	7	400	31.3	43.6	5.4	3.8–12.1					
600	2	1	600	20.1	15.6	20.1	9.1–31.1					
800	15	10	800	42.8	22.3	45.0	10.7–83.5					
1000	10	6	1000	53.1	35.0	44.7	13.3–166.6					
Creatinine clearance (mL/min)												
<70	5		560 ± 219	55.3	29.8	45.8	31.1–100.4	76.7	18.2	69.4	60.0–100.4	.015*
>70–<100	15		800 ± 226	41.0	31.6	38.4	1.8–122.1	44.1	40.8	30.7	3.6–145.8	
>100	14		800 ± 175	38.7	31.6	33.4	5.1–116.0	41.1	38.2	31.3	5.1–116.6	
Need for epogen												
Yes	**	11	820 ± 194	36.0	26.7	34.2	4.3–100.4	61.2	44.0	40.7	25.4–145.8	.2
No	**	11	685 ± 232	50.9	36.5	40.9	1.8–122.1	48.4	30.2	54.4	3.6–97.7	
Coadministration of other drugs												
Proton pump inhibiters used	20	9	790 ± 182	47.5	35.4	45.8	4.3–122.1	47.2	35.9	36.4	3.4–120.0	
Proton pump inhibiters not used	14	13	729 ± 267	36.1	26.1	30.6	1.8–83.5	40.3	39.1	30.5	3.6–145.8	
HAART used	5	3	800 ± 0	87.4	39.4	100.4	26.8–12.1	87.1	39.4	100.4	26.8–12.1	
HAART not used	29	19	785 ± 233	34.4	22.9	34.8	1.8–83.5	38.5	34.8	35.8	3.4–145.8	.000
HCV RNA cleared												
No	**	7	657 ± 276	42.2	40.3	31.1	1.8–76.2	39.0	30.0	30.2	3.6–97.7	.3
Yes	**	9	725 ± 212	52.5	29.8	42.0	13.2–100.4	68.9	43.6	61.2	26.8–145.8	

*Significant when creatinine a clearance <70.
**Highest value used when more than one observation.

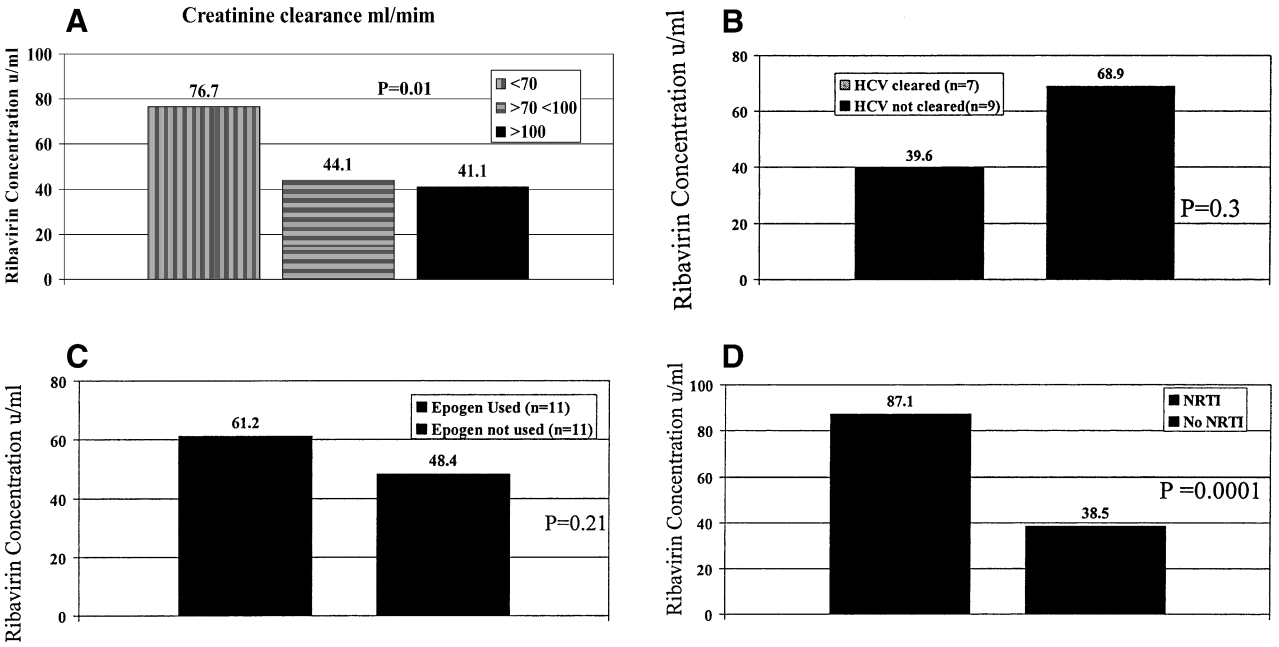

Fig 2. Mean ribavirin dose normalized concentration (μg/mL). **(A)** In relation to creatinine clearance <70, >70, <100, and >100. **(B)** Clearance of HCV RNA (n = 7) and non responders (n = 9). **(C)** Erythropoietin factors used (n = 11) and not used (n = 11). **(D)** Use of NRTI.

DISCUSSION

HCV infection resulting in end-stage liver failure is the most common indication for LTx in the United States.[1] Disease recurrence is uniform after successful transplantation.[2,3,14] Combination therapy of pegylated interferon and ribavirin has resulted in improved, sustained clearance of virus in nearly 50% of cases.[4,5] However, the major side effect of ribavirin is anemia and dose modification or withdrawal is necessary in 40% to 80% of cases.[6–9] Ribavirin is primarily cleared by kidney and has a long half-life.[15–17] We have in the past suggested modification of ribavirin doses based on renal function to reduce hemolysis.[11] Similar observations have been made by Bruchfield et al.[10] Based on high withdrawal rate and dose modifications reported in the literature,[10,11] we decided to examine the plasma concentration of ribavirin from left over blood samples collected to measure tacrolimus, on an institutional review board approved protocol. The intention was to correlate ribavirin concentration with its side effects, renal function, and look at other variables including the effect of coadministered medications in post-LTx patients. We found wide variations in ribavirin levels. Since the majority of the drug is bound to red cells, we also estimated simultaneous ribavirin concentration in whole blood in 16 samples. To our surprise, the concentration in whole blood and plasma was similar, unlike tacrolimus where concentrations are 10 times higher in whole blood than plasma.[18] Whether tacrolimus preferentially binds to red cells and inhibits binding of ribavirin is not clear from this study. Mean concentration tended to be higher with higher daily dosage of ribavirin. Since patients were on different doses of ribavirin, the concentrations were normalized to daily dose of ribavirin 800 mg/d for comparison. The mean concentration of ribavirin was significantly higher when creatinine clearance was below 70 mL/min compared to patients who had creatinine of above 70 mL/min. However, contrary to expectations, patients who required erythropoitin for hemolysis were on higher doses but had lower mean concentrations of ribavirin than patients who did not have significant hemolysis. However this was not significant with dose-normalized ribavirin concentrations. Interestingly, mean creatinine clearance was almost identical in both groups. It is possible that other mechanisms of hemolysis are involved rather than plasma concentration of ribavirin alone. Also, seven patients who cleared HCV RNA had lower mean dose-normalized concentrations compared to those who did not clear virus with wide variations in ribavirin concentration. This did not reach statistical significance. We postulate that metabolites of ribavirin rather than ribavirin may be responsible for hemolysis and efficacy.[19] When the role of coadministered medication in posttransplant patients was examined, the concentration of ribavirin was significantly higher in these patients who were on NRTI treatment compared to who were not on NRTI treatment. Profound drug interaction between protease inhibitors in HAART regimen and immunosuppressive agents has been described due to the cytochrome P450 enzyme system.[20–22] Drug interaction of ribavirin and NRTI has been demonstrated before.[23] This poses a challenge to clinicians who deal with LTx patients,

infected both with HIV and HCV. Longitudinal studies of ribavirin concentrations in the same patient population resulted in one interesting finding, not previously reported. Proton pump inhibitors, in some way, may interfere with ribavirin absorptions. That may take much longer to achieve steady-state concentrations in these individuals. The mechanism is not clear but changes in gastric pH (with proton pump inhibitors) may interfere with ribavirin absorption. Further study on this phenomenon is required in vivo and in vitro.

In conclusion, there was wide variation in ribavirin plasma concentration. Plasma and whole blood concentrations were similar. Patients with higher doses had higher plasma concentrations. Patients with renal dysfunction had significantly higher drug concentrations. However, response to ribavirin and peg interferon, as well as need for erythropoietin factor did not correlate with ribavirin concentration. Also, patients who received NRTI had significantly higher concentrations. More prospective controlled studies and kinetic profiles are needed to understand efficacy and toxicity of ribavirin including phosphorylated metabolites of ribavirin.

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