ORIGINAL RESEARCH ARTICLE

Adverse Events Associated with High-Dose Ribavirin: Evidence from the Toronto Outbreak of Severe Acute Respiratory Syndrome

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Study Objectives. To distinguish adverse events related to ribavirin therapy from those attributable to severe acute respiratory syndrome (SARS), and to determine the rate of potential ribavirin-related adverse events.

Design. Retrospective cohort study.

Setting. Hospitals in Toronto, Ontario, Canada.

Patients. A cohort of 306 patients with confirmed or probable SARS, 183 of whom received ribavirin and 123 of whom did not, between February 23, 2003, and July 1, 2003. Of the 183 treated patients, 155 (85%) received very high–dose ribavirin; the other 28 treated patients received lower-dose regimens.

Measurements and Main Results. Data on all patients with SARS admitted to hospitals in Toronto were abstracted from charts and electronic databases onto a standardized form by trained research nurses. Logistic regression was used to evaluate the association between ribavirin use and each adverse event (progressive anemia, hypomagnesemia, hypocalcemia, bradycardia, transaminitis, and hyperamylasemia) after adjusting for SARS-related prognostic factors and corticosteroid use. In the primary logistic regression analysis, ribavirin use was strongly associated with anemia (odds ratio [OR] 3.0, 99% confidence interval [CI] 1.5–6.1, $p<0.0001$), hypomagnesemia (OR 21, 99% CI 5.8–73, $p<0.0001$), and bradycardia (OR 2.3, 99% CI 1.0–5.1, $p=0.007$). Hypocalcemia, transaminitis, and hyperamylasemia were not associated with ribavirin use. The risk of anemia, hypomagnesemia, and bradycardia attributable to ribavirin use was 27%, 45%, and 17%, respectively.

Conclusions. High-dose ribavirin is associated with a high rate of adverse events. The use of high-dose ribavirin is appropriate only for the treatment of infectious diseases for which ribavirin has proven clinical efficacy, or in the context of a clinical trial. Ribavirin should not be used empirically for the treatment of viral syndromes of unknown origin.

Key Words: ribavirin, adverse events, severe acute respiratory syndrome, SARS, hemolytic anemia.

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Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole) is a synthetic purine nucleotide analog with in vitro activity against a wide range of RNA and DNA viruses.[1] Ribavirin is used for the treatment

of chronic hepatitis C (in combination with interferon-α),[2] severe respiratory syncytial virus pneumonitis,[3] and some viral hemorrhagic fevers, particularly Lassa fever.[4–9] Its mechanism of action is not fully understood.[10]

Ribavirin was used empirically early in the outbreak of severe acute respiratory syndrome (SARS) because of its broad-spectrum antiviral activity.[11, 12] In Toronto, Ontario, Canada, most patients seen during the initial phase of the outbreak were treated with high-dose intravenous ribavirin, based on a protocol recommended for the treatment of hemorrhagic fever.[8] However, the initial in vitro studies of ribavirin suggested that inhibition of viral replication would not be possible at clinically achievable doses.[13–16] Studies of the clinical efficacy of ribavirin in patients with SARS were inconclusive,[11, 17–20] and significant adverse events were reported, including severe hemolysis.[17, 21–23] As a result, as the first phase of the outbreak ended, clinicians in Toronto stopped using ribavirin. Unlike other cities, the Toronto SARS outbreak was biphasic, with a large cluster of cases occurring after the use of ribavirin was discontinued.[24] The Toronto outbreak was unique in that it had significant numbers of patients treated or not treated with ribavirin. This provided an opportunity to distinguish ribavirin-induced adverse events from adverse events directly attributable to SARS and to estimate the frequency of SARS adverse events in a large group of patients treated with high-dose ribavirin.

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Methods

Study Design and Population

This was a retrospective cohort study that captured data on adverse events for all adult patients (age ≥ 16 yrs) with confirmed or probable SARS who were admitted to a hospital during the Toronto SARS outbreak between February 23, 2003, and July 1, 2003. Patients were considered to have probable SARS if they had a compatible clinical illness (fever, nonproductive cough, or dyspnea), an exposure to SARS (direct contact with a patient who had a known SARS case, travel to a SARS-endemic area, or time spent at an institution where SARS transmission was occurring, within 12 days of symptom onset), and an infiltrate on chest radiograph. Patients were considered to have confirmed SARS if they had a compatible clinical illness, exposure to SARS, and a positive microbiologic test (positive acute or convalescent serology, or positive polymerase chain reaction for SARS coronavirus from clinical or pathologic specimens). The serologic and microbiologic methods used have been described previously.[25, 26]

Definitions of Ribavirin Exposure and Primary and Secondary Outcomes

Ribavirin use was the exposure of interest. Patients were considered exposed if they received at least one dose of ribavirin before the onset of the adverse event. Patients were considered not exposed if they did not receive ribavirin before the onset of the outcome.

The primary outcomes examined were adverse events of ribavirin (defined in Appendix 1): progressive anemia, hypomagnesemia, hypocalcemia, bradycardia, transaminitis, and hyperamylasemia. These outcomes were selected either because they were known ribavirin-induced adverse events or because they were considered to be possible ribavirin-induced adverse events based on data from noncontrolled studies of ribavirin-treated patients with SARS (Appendix 2[22, 27–33]) and because they could be defined using clinical or laboratory parameters that were measured routinely in both treated and nontreated patients.

Secondary outcomes of interest were evidence of hemolysis, clinically significant (symptomatic) bradycardia, tetany or muscle spasm, hepatitis, and pancreatitis (Appendix 1).

Table 1. Baseline Characteristics of the Study Patients

Characteristic	Patients Treated with Ribavirin (n=183)	Patients Not Treated with Ribavirin (n=123)	p Value[a]
	Median (interquartile range)		
Age (yrs)	44 (34–56)	45 (36–57)	0.18
Admission laboratory tests			
White blood cell count (x 10^3/mm^3)	5.2 (3.7–6.9)	5.6 (4.3–6.7)	0.20
Absolute neutrophil count (x 10^3/mm^3)	3.5 (2.4–5.2)	4.0 (2.9–5.2)	0.017
Absolute lymphocyte count (x 10^3/mm^3)	0.9 (0.70–1.2)	1.0 (0.75–1.3)	0.28
Lactate dehydrogenase level (U/L)	369 (202–617)	224 (174–329)	<0.0001
	No. (%) of Patients		
Sex			0.24
Female	110 (60)	82 (67)	
Male	73 (40)	41 (33)	
Health care workers	94 (51)	57 (46)	0.39
Comorbidity present	28 (15)	19 (15)	0.97
Admission oxygen saturation < 95%	86/182 (47)	40/121 (33)	0.014
Initial chest radiographic findings			
Pulmonary infiltrate	123/179 (69)	78 (63)	0.34
Bilateral pulmonary infiltrate	49/179 (27)	28 (23)	0.37
Other treatment			
Corticosteroids	93 (51)	81 (66)	0.009
Outcomes			
Mechanical ventilation	27 (15)	19/123 (15)	0.88
Death	20 (11)	10 (8)	0.42

[a]p values derived from Wilcoxon rank sum test for continuous variables and χ^2 test for categoric variables.

Data Collection and Ethics

Data were abstracted from charts and electronic databases onto a standardized form by trained research nurses. Data were double entered into an Access database (Microsoft Corp., Redmond, WA). The study was approved by the research ethics boards at all participating hospitals, at McMaster University, Hamilton, Ontario, and at the University of Toronto, Toronto, Ontario, Canada.

Statistical Analysis

Analysis was conducted with use of SAS software, version 8 (SAS Institute, Cary, NC). For the univariate analyses, continuous variables were compared by using the Wilcoxon rank sum test or the two-sample *t* test as appropriate. Categoric variables were compared by using the χ^2 or Fisher exact test, as appropriate. The attributable risk for each adverse event was determined by subtracting the rate of the adverse events in the nontreated patients from its rate in the treated patients. We checked for the presence of a dose-response effect by reclassifying the exposure as very high dose, high dose, or no ribavirin received. A regimen consisting of a 2-g intravenous loading dose followed by 1 g intravenously every 8 hours for 4 days, followed by 500 mg intravenously every 6 hours for 3 days was considered very high–dose treatment. All other regimens were considered high-dose treatment. The proportion of very high–dose–treated, high-dose–treated, and nontreated patients with an outcome was examined graphically and with the Cochrane-Armitage trend test.

The primary analysis was a multivariate logistic regression analysis that examined the association between ribavirin use and adverse events, adjusting for factors predictive of severe SARS and corticosteroid use. The predictors included in the model were age, comorbidity, oxygen saturation, chest radiographic findings, absolute neutrophil count, and lactate dehydrogenase level, measured on admission. These factors are associated with progressive respiratory failure, the need for mechanical ventilation, and death from SARS.[17, 19, 34–39]

Multiple imputation was used to impute missing values for the predictive factors in the model, as this approach has been shown to be more powerful and less biased than excluding from the analysis all patients with one or more missing predictors.[40–42] Because we tested five hypotheses in our primary analysis (i.e., the association of ribavirin with each of five adverse

Table 2. Frequency of Adverse Events

Adverse Event	Patients Treated with Ribavirin (n=183)	Patients Not Treated with Ribavirin (n=123)	p Value[a, b]
Progressive anemia	103/181 (57)	37/125 (30)	<0.0001
Bradycardia	63/183 (34)	21/123 (17)	0.0009
Hypomagnesemia	91/182 (50)	6/124 (5)	<0.0001
Hypocalcemia	96/175 (55)	50/131 (38)	0.0038
Transaminitis	40/183 (22)	15/123 (12)	0.031
Hyperamylasemia	20/183 (11)	5/123 (4)	0.032[c]

Due to the timing of adverse events in relation to the start of ribavirin therapy, the number of untreated patients for each event differs slightly. Numbers in parentheses are percentages.
[a]From χ^2 test unless otherwise indicated.
[b]Threshold for significance = 0.01 based on Bonferroni correction.
[c]Fisher exact test.

events), to maintain an α of 0.05, we used the Bonferroni correction to lower the p value threshold for statistical significance from 0.05 to 0.01. Confidence intervals (CIs) were also adjusted from 95% to 99%. This approach minimizes the risk of identifying a chance association due to multiple-hypotheses testing.[43]

Results

Description of the Cohort

The cohort consisted of 306 patients with confirmed (258 patients) or probable (48 patients) SARS. Ribavirin was given to 183 (60%) of the 306 patients and its use was equivalent in confirmed versus probable cases (59% vs 63%, p=0.67). In the first phase of the outbreak, 182 (85%) of 215 patients received ribavirin. In the second phase, only 1 (1%) of 91 patients received ribavirin. Corticosteroid therapy was the only other specific therapy for SARS widely used during the outbreak. Overall, of the 306 patients, 42 (14%) received no treatment, 90 (29%) received ribavirin, 81 (26%) received corticosteroids, and 93 (30%) received both.

Ribavirin was started promptly, with 83% of patients receiving their first dose within 48 hours of admission. The mean ± SD total dose received was 23.3 ± 9.4 g, and the median duration of treatment was 7 days (interquartile range [IQR] 5–9 days). The full treatment course was completed in 102 (56%) of 183 patients. Reasons for discontinuation among the 81 patients who did not complete their course of therapy included adverse events attributed to treatment (28 patients), clinical improvement (15), death (5), changing treatment guidelines (5), patient refusal (2), or no reason documented (26). Adverse events documented as a cause for drug discontinuation included anemia or hemolysis (19 patients), drug-induced hepatitis or transaminitis (5), bradycardia (1), atrial fibrillation (1), nausea (1), and unspecified (1).

Overall, 155 (85%) of 183 treated patients received very high–dose ribavirin; the other 28 treated patients received a variety of lower-dose regimens. The mean total dose received was 25.2 g in the very high–dose group and 12.9 g in the lower-dose group. The rate of discontinuation was similar in both groups (56% vs 54%, p=0.80).

Baseline characteristics of the ribavirin-treated and nontreated patients are shown in Table 1. Ribavirin-treated patients were more likely to be hypoxemic (47% vs 33%, p=0.014), have a higher baseline lactate dehydrogenase level (369 vs 224 U/L, p<0.0001), and have a lower absolute neutrophil count (3.5 vs 4.0, p=0.017). The median age was similar in both groups (44.2 vs 45.3 yrs, p=0.18). Outcomes were similar in both groups, both in terms of the need for mechanical ventilation (15% vs 15%, p=0.88) and the case fatality rate (11% vs 8%, p=0.42).

Evidence of Association of Adverse Events with Ribavirin Use

In the univariate analysis, all of the adverse events occurred more often in ribavirin-treated patients. The strongest associations were seen with progressive anemia and hypomagnesemia (Table 2, Figure 1). Bradycardia and hypocalcemia were also significantly more common among ribavirin-treated patients. Ribavirin use was not statistically significantly associated with transaminitis or hyperamylasemia. Only progressive anemia and hypomagnesemia had graphical

evidence of a dose-response effect (Figure 2).

In the primary adjusted analysis, ribavirin remained strongly associated with hypomagnesemia (odds ratio [OR] 21, 99% CI 5.8–73, p<0.0001) and progressive anemia (OR 3.0, 99% CI 1.5–6.1, p<0.0001; Table 3). A more modest association also persisted with bradycardia (OR 2.3, 99% CI 1.0–5.1, p=0.007). Ribavirin did not appear significantly associated with hypocalcemia (OR 1.8, 99% CI 0.91–3.4, p=0.028) or with transaminitis (OR 1.8, 99% CI 0.74–4.6, p=0.08) in the primary analysis. Hyperamylasemia was not examined as there were insufficient numbers to allow meaningful multivariate analysis.

Table 3. Analysis of Association of Ribavirin and Five Adverse Events After Adjusting for Corticosteroid Use and SARS-Related Prognostic Factors in a Multivariate Logistic Regression Model

Adverse Event	Ribavirin Effect OR (99% CI)[a]	p Value[b]
Progressive anemia	3.0 (1.5–6.1)	<0.0001
Bradycardia	2.3 (1.0–5.1)	0.007
Hypomagnesemia	21 (5.8–73)	<0.0001
Hypocalcemia	1.8 (0.91–3.4)	0.028
Hepatitis, biochemical (transaminitis)	1.8 (0.74–4.6)	0.08

SARS = severe acute respiratory syndrome; OR = odds ratio; CI = confidence interval.
[a]Adjusted for corticosteroid use, age, comorbidity, and the following variables measured at admission: oxygen saturation, extent of infiltrate on chest radiograph, absolute neutrophil count, and lactate dehydrogenase level.
[b]Threshold for significance = 0.01 based on Bonferroni correction.

Frequency, Timing, and Clinical Significance of Adverse Events Associated with Ribavirin Use

Ribavirin use was not associated with hypocalcemia or transaminitis, both of which appear to be SARS-related effects. We therefore focused on the frequency, timing, and clinical significance of ribavirin-induced anemia, hypomagnesemia, and bradycardia.

Progressive anemia occurred in 103 (57%) of 181 ribavirin-treated patients, and hemolysis was confirmed in 84 (82%) of the 103 patients. As progressive anemia occurred in 37 (30%) of 125 nontreated patients, the risk of anemia attributable to ribavirin use was 27%. Despite the higher frequency of progressive anemia among ribavirin-treated patients, the need for blood transfusions was similar in treated versus nontreated patients (12% vs 10%, p=0.48). The mean ± SD decrease in hemoglobin level was 3.0 ± 1.9 g/dl among treated patients and 1.9 ± 1.9 g/dl among nontreated patients (p<0.001). The median time from the initiation of treatment to the development of progressive anemia was 6 days (IQR 3–8 days).

Hypomagnesemia occurred in 91 (50%) of 182 treated patients and 6 (5%) of 124 nontreated patients, for an attributable risk of 45%. The mean ± SD decrease in magnesium level among treated patients was 0.34 ± 0.34 mEq/L, and the median time from the initiation of treatment until occurrence of hypomagnesemia was 2 days (IQR 1–4 days).

Tetany occurred in 5 (3%) of 182 treated patients and 2 (2%) of 124 nontreated patients (p=0.71). Patients with tetany all had evidence of electrolyte imbalance during their hospitalization, with 5 having both hypocalcemia and

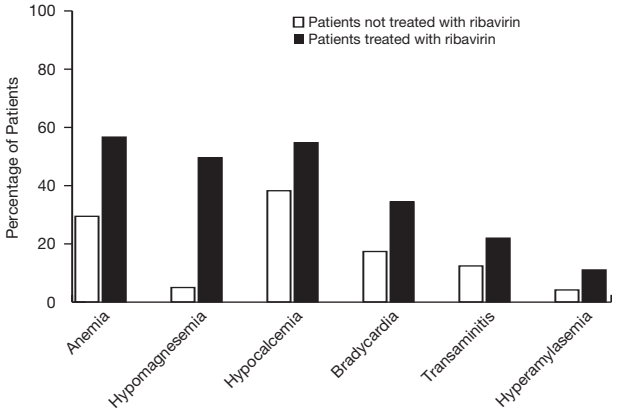

Figure 1. Association between adverse events and ribavirin use.

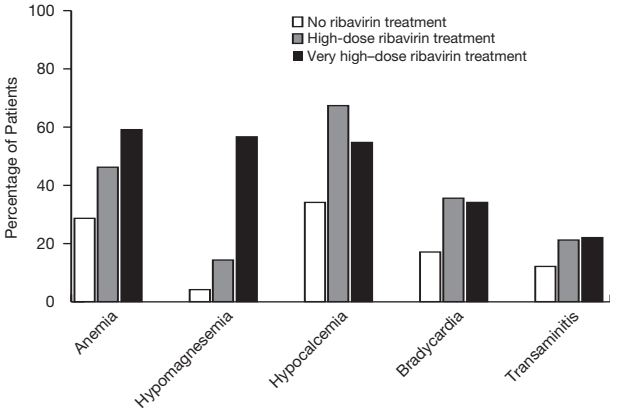

Figure 2. Dose-response effect according to ribavirin exposure. Associations with ribavirin use for all adverse events except transaminitis were statistically significant based on the Cochrane-Armitage trend test, but only anemia and hypomagnesemia demonstrated a graphic dose-response trend.

hypomagnesemia, 1 having hypomagnesemia alone, and 1 having hypocalcemia alone. Of the 4 cases that had magnesium and calcium levels obtained on the day that tetany occurred, 4 of 4 had hypocalcemia and 2 of 4 had hypomagnesemia.

Bradycardia occurred in 63 (34%) of 183 ribavirin-treated patients and 21 (17%) of 123 nontreated patients, for an attributable risk of 17%. Bradycardia was considered clinically significant in 24 (38%) of the 63 bradycardic patients. The median time from initiation of treatment to bradycardia was 3 days (IQR 2–4 days).

Discussion

Although high-dose ribavirin is recommended for the treatment of Lassa fever and may be useful for some other hemorrhagic fever syndromes, most data on adverse events associated with oral or parenteral ribavirin come from studies of lower doses of oral ribavirin used in the treatment of chronic hepatitis C.[27, 28]

We report the frequency of adverse events in 183 patients treated with high-dose ribavirin during the Toronto SARS outbreak. Although other studies that examined ribavirin-related adverse events in treated patients with SARS have been published, most were noncontrolled[17, 22, 34] or had small control groups[44] (i.e., seven patients). To our knowledge, our study is the first study with a control group large enough to allow differentiation between ribavirin-related adverse events and the manifestations of SARS itself.

Our results confirm that progressive hemolytic anemia is a common adverse event of high-dose ribavirin. Although progressive anemia occurred among nontreated patients (presumably due to SARS, severe illness, and the effects of hospitalization), clinically important declines in hemoglobin level were far more common in patients treated with ribavirin.

Our finding that 57% of patients developed progressive anemia (largely associated with hemolysis) is substantially higher than the 9–19% rate seen in ribavirin-treated patients with hepatitis C but is consistent with the 49–73% reported in previous noncontrolled studies of ribavirin-related adverse events in patients with SARS.[17, 22, 34, 44] These results are misleading, however, given that 30% of nontreated patients in our cohort also developed anemia. The rate of excess cases of anemia (i.e., attributable risk) was 27%, and this is a more accurate estimate of the impact of ribavirin therapy, although it may still be an overestimate given that the nontreated group appeared to have milder SARS than the treated group and would be expected to have less SARS-related anemia. Despite a previous study suggesting that 17% of ribavirin-treated patients required blood transfusions,[22] our data did not demonstrate a higher transfusion requirement in the treated group.

Before the SARS outbreak, hypocalcemia and hypomagnesemia were not recognized as adverse effects of ribavirin.[22, 29] However, two early case series of SARS cases in Toronto both suggested that hypocalcemia and hypomagnesemia were common in patients with SARS and may be due to ribavirin.[21, 22] In the first report, 2 of 14 ribavirin-treated patients developed tetany associated with severe hypomagnesemia (magnesium levels < 0.2 mEq/L) and hypocalcemia (corrected calcium levels ≤ 3.68 mg/dl).[21] In the second report, 46% (35/76) of ribavirin-treated patients developed hypomagnesemia and 58% (36/62) developed hypocalcemia.[22] In that study, hypomagnesemia, but not hypocalcemia, was related to the dose of ribavirin received. A larger study of the first phase of the Toronto outbreak demonstrated that hypocalcemia and hypomagnesemia occurred in 70% and 57% of patients, respectively, during hospitalization but noted that 60% had hypocalcemia on admission.[17] Studies from Hong Kong, China, Singapore, and Taiwan do not comment on hypocalcemia and hypomagnesemia associated with ribavirin use, although much lower doses of ribavirin were used in these areas.[18, 20, 34, 45–47]

Our results clarify these findings. First, we have demonstrated that hypomagnesemia is strongly associated with the use of high-dose ribavirin and is not a disease-related effect. The association was dramatic: less than 5% of nontreated patients developed hypomagnesemia, compared with 50% of treated patients. Furthermore, the estimated OR in the primary adjusted analysis was 21 (99% CI 5.8–73) and the effect appeared to be dose dependent. These results are consistent with the findings of the previous studies.[17, 21, 22]

Our study, however, suggests that hypocalcemia is a disease-related effect and was not caused by ribavirin. Hypocalcemia occurred frequently in nontreated patients, was not dose dependent, and was not statistically significantly associated with ribavirin treatment in the primary adjusted analysis. These results are also consistent with the previous studies in that the effect did not appear dose dependent[22] and was frequently present before the initiation of ribavirin therapy.[17]

Furthermore, hypocalcemia is known to be associated with sepsis and critical illness.[48, 49]

Although we identified seven cases of tetany, all of which were associated with hypocalcemia and/or hypomagnesemia, they occurred with approximately equal frequency in the ribavirin-treated and nontreated groups. Although associated with electrolyte disturbances, it remains unclear what role, if any, ribavirin played in these adverse events.

Cardiovascular effects, particularly bradycardia, have been associated with ribavirin use.[29] In our analyses, bradycardia was associated with ribavirin use in both the univariate and multivariate analysis, although a dose-response effect was not seen. Bradycardia was clinically significant in one third of cases.

Transaminitis appeared to be a SARS-related effect rather than a ribavirin effect and was not statistically significantly associated with ribavirin use in either the univariate or the primary multivariate analyses. This finding is consistent with a case series describing histologic changes in the liver that were more consistent with coronavirus-induced hepatitis than with drug-induced hepatitis.[50]

Finally, there was a trend toward higher amylase levels among ribavirin-treated patients, but too few patients had elevated levels to allow multivariate analysis and no patient had clinically defined pancreatitis. Although these results cannot rule out pancreatitis as an uncommon adverse effect of high-dose ribavirin therapy, pancreatitis did not occur in this cohort.

Our study has several limitations. Data collection was retrospective, and the potential for several types of bias exist. Clinicians aware of potential ribavirin adverse events may have tested for, or recorded, these events more frequently in ribavirin-treated patients. Similarly, data abstractors may have searched more diligently for adverse events in the ribavirin-treated patients. In addition, if patients with more severe SARS were more likely to be treated, disease-related effects would appear to be associated with treatment (selection bias). We attempted to minimize these biases by using study end points that were objective and were measured routinely in both treated and nontreated patients. Thus, anemia was considered a primary outcome, rather than hemolysis, as it could be defined based only on hemoglobin levels, which were routinely measured in all patients, as opposed to haptoglobin levels, which were ordered primarily in ribavirin-treated patients. To control for selection bias, we used logistic regression to adjust for factors predictive of severe SARS. Although these approaches cannot remove all of the bias inherent in a retrospective study, the results represent an improvement on previous reports of adverse events in patients treated with high-dose ribavirin that examined only small numbers of patients and/or failed to include a control group or adjust for confounding factors.

Conclusion

Our study results confirm that high-dose ribavirin can cause hemolytic anemia and bradycardia and demonstrated for the first time, to our knowledge, a striking association between high-dose ribavirin use and hypomagnesemia. Previous studies suggest that 10% of patients with hepatitis C who were receiving ribavirin discontinue treatment due to cardiovascular or respiratory effects secondary to severe anemia.[29] We did not include cardiac or respiratory outcomes in our study, primarily because cardiac events were rarely reported in the cohort and the potential respiratory effects of ribavirin were impossible to distinguish from the primary manifestations of SARS itself. Thus, the clinical impact of these effects remains uncertain, although clinical markers including survival, transfusion requirements, and tetany were not more common among ribavirin-treated patients. However, our cohort was largely made up of young and previously healthy health care workers; only 15% of the cohort had any comorbid illness and only 5% had a history of cardiac or respiratory disease. In an older cohort with more comorbidity, the impact of ribavirin-associated hemolytic anemia may have been more severe.

The ribavirin doses used for SARS in Toronto are at the boundary of what appears to be the maximum clinically tolerable dose. Given the clear association of high-dose ribavirin with several potentially severe adverse events and the high frequency of these events, several recommendations appear appropriate. High-dose oral or parenteral ribavirin should be used only in a monitored setting and only in patients without cardiac or respiratory conditions that would be exacerbated by an acute decline in hemoglobin level. Previous recommendations that high-dose oral ribavirin should be provided in the event of a mass casualty situation relating to a natural outbreak of an unknown hemorrhagic fever

syndrome or a deliberate bioterrorist attack should be reassessed given these data.[8] Furthermore, the use of ribavirin outside of clinical trials should be restricted to the treatment of life-threatening conditions for which ribavirin has been demonstrated to improve outcomes. In the event of another SARS outbreak, the widespread use of ribavirin does not appear justified given equivocal in vitro and in vivo evidence of efficacy and clear evidence of toxicity. When outbreaks occur due to novel viral pathogens, we believe that the early use of high-dose ribavirin, even in the context of a controlled clinical trial, is not justifiable until the virus is isolated, in vitro testing demonstrates ribavirin activity at clinically achievable doses, and the natural history of the illness suggests that the potential benefits of ribavirin outweigh the harms.

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Appendix 1. Definition of Adverse Events

Adverse Event	Definition
Primary	
Progressive anemia	Decrease in hemoglobin level of 2 g/dl
Hypomagnesemia	Decrease in magnesium level from ≥ 1.4 mEq/L to < 1.4 mEq/L, or a decrease of 25% if < 1.4 mEq/L at baseline
Hypocalcemia	Decrease in corrected calcium level from ≥ 8.8 mg/dl to < 8.8 mg/dl, or a decrease of 25% if < 8.8 mg/dl at baseline
Bradycardia	Heart rate < 55 beats/minute
Transaminitis	Increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels to 2 times the upper limit of normal, or a doubling of the AST and ALT level if abnormal at baseline
Hyperamylasemia	Increase in amylase level to 2 times the upper limit of normal, or a doubling of amylase level if abnormal at baseline
Secondary	
Hemolysis	Progressive anemia associated with any of the following: haptoglobin level < 38 mg/dl, reticulocyte count > 110 reticulocytes/1000 erythrocytes, or total bilirubin level > 1.5 times baseline
Tetany or muscle spasm	Note on chart indicating that patient had tetany or severe muscle spasms that required evaluation and treatment
Clinically significant bradycardia	Bradycardia associated with hypotension or symptoms (dizziness, presyncope, syncope, lightheadedness, or chest pain)
Hepatitis	Transaminitis associated with any two of the following: jaundice, nausea, vomiting, anorexia, malaise, or abdominal pain
Pancreatitis	Hyperamylasemia associated with abdominal pain

Appendix 2. Adverse Events Associated with Oral or Parenteral Ribavirin Use as Reported in the Literature

Adverse Event	Comment
Anemia, hemolysis	Anemia appears dose and time dependent and is reversible.[27, 29] Highest risk with dosages above 1–1.2 g/day[27, 29] administered for more than 10 days.[29] With oral ribavirin used for the treatment of chronic hepatitis C, 9–19% develop anemia, which occurs within 1–2 weeks of starting therapy and stabilizes by 4 weeks.[27–29] Average maximum decrease in hemoglobin level from baseline among those with anemia was 2.6–3.1 g/dl.[29]
Cardiovascular effects	Worsening of coronary artery disease and chronic heart failure have been associated with oral and parenteral ribavirin primarily as secondary effects triggered by severe anemia.[29] (Bradycardia, hypotension, and cardiac arrest have been reported with inhaled ribavirin.[29])
Seizures	Reported with parenteral ribavirin.[29]
Asthenia	Reported with parenteral ribavirin.[29]
Transaminitis	Reported with oral and parenteral ribavirin.[29]
Hypomagnesemia	Reported from a single noncontrolled study of oral and parenteral ribavirin use in severe acute respiratory syndrome (SARS).[22]
Hypocalcemia	Small study showed increased rate of hypocalcemia in patients receiving oral ribavirin for hepatitis C,[30] or receiving parenteral therapy for measles pneumonitis[31] or SARS.[22]
Pancreatitis	Reported from an open-label study in Hanta virus pulmonary syndrome.[32]
Teratogenicity	Significant teratogenicity reported in animal studies.[29]
Other rarely reported events	Rash, pruritus, alopecia, dry skin, taste disturbance, nausea, vomiting, diarrhea, dyspnea, rhinitis, pharyngitis, dizziness, headache, sleep disturbance, irritability, arthralgia, thyroid disorders, hyperuricemia.[28, 33]