

# Ribavirin in the treatment of SARS: A new trick for an old drug?

Gideon Koren, Susan King, Sandra Knowles, Elizabeth Phillips

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§ See related article pages 1245, 1259, 1265, 1294

The dramatic outbreak of severe acute respiratory syndrome (SARS) has led to the use of high-dose intravenous and oral ribavirin in patients affected with this disorder. Ribavirin, a nucleoside analogue with broad antiviral activity, was discovered in 1970 by ICN Pharmaceuticals. In Canada, ribavirin is licensed for the treatment of respiratory syncytial virus (RSV) infection in infants and, in combination with interferon  $\alpha 2b$ , hepatitis C. In view of the limited circumstances in which it is prescribed, most physicians are not familiar with its pharmacology, dosing and safety. In this article we summarize this information for the benefit of health care professionals who may be involved with patients receiving ribavirin for treatment or prevention of SARS. We also review emerging data on the potential efficacy of ribavirin against the SARS virus, a new mutant of coronavirus.

## Clinical pharmacology

Ribavirin is a purine nucleoside analogue. Although its mechanism of action is still debated, it prevents replication of a large number of RNA and DNA viruses by inhibiting the enzyme inosine monophosphate dehydrogenase, which is required for the synthesis of guanosine triphosphate. The final step in this chain of events is lethal mutagenesis of the RNA genome.<sup>1</sup> In vitro inhibition of RSV, influenza viruses and parainfluenza viruses is achieved at ribavirin concentrations of 3-10  $\mu\text{g/mL}$ .

The plasma elimination of ribavirin occurs in 2 phases, the first with a relatively short half-life of 2 hours, the second with a much longer terminal half-life of 16-164 hours. The active metabolite of the drug, ribavirin triphosphate, concentrates in erythrocytes and leaches out slowly, with a half-life of 40 days. Ribavirin has 2 metabolic pathways: a reversible phosphorylation pathway and a degradative pathway involving deribosylation and amide hydrolysis.<sup>2</sup> Ribavirin is eliminated primarily by renal excretion, and dose reductions are required in patients with renal insufficiency (Box 1).

Ribavirin can be given orally (with an absolute bioavailability of 40% to 50%), intravenously or as an aerosol. In adults an oral dose of 600 mg yields peak plasma levels of 1.3  $\mu\text{g/mL}$ , an intravenous dose of 1000 mg results in mean concentrations of 24  $\mu\text{g/mL}$ , and the aerosol preparation

appears in the plasma at levels of 0.2 to 1  $\mu\text{g/mL}$  (in this case, levels of the drug in respiratory secretions can be up to 1000-fold higher). The recommended dosage regimens for adults with SARS are presented in Box 1, and recommendations for children with SARS appear in Box 2.

## Applications

Aerosolized ribavirin was first used for RSV bronchiolitis and pneumonia in young hospitalized children, in whom it had a modest effect relative to that of placebo.<sup>3</sup> It has

### Box 1: Current recommendations for use of ribavirin in adults with probable or suspected severe acute respiratory syndrome (SARS)\*

The efficacy of ribavirin in treating SARS is not known, but if ribavirin is being started, use an intravenous (IV) formulation.

#### **Creatinine clearance > 60 mL/min**

400 mg IV every 8 hours for 3 days, then 1200 mg orally (with food) twice daily for 7 days

#### **Creatinine clearance 30-60 mL/min**

Daily dose is reduced by 50% from dose for patients with creatinine clearance > 60 mL/min

300 mg IV every 12 hours for 3 days, then 600 mg orally (with food) twice daily for 7 days

#### **Creatinine clearance < 30 mL/min**

Daily dose is reduced by 75% from dose for patients with creatinine clearance > 60 mL/min

300 mg IV every 24 hours for 3 days, then 600 mg orally (with food) once daily for length of therapy (at present, length of therapy is empirical)

\*The treatment dose of ribavirin has been reduced significantly from earlier recommendations because of a lack of information to support the in vitro efficacy of ribavirin against the coronavirus that has been implicated in SARS, as well as concerns about side effects that have been observed in patients treated with high-dose IV and oral ribavirin.

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### Availability of ribavirin

Parenteral ribavirin is not approved for sale in Canada and is available only through the Special Access Programme (SAP), Therapeutic Products Directorate, Health Canada. To request the drug, Canadian physicians should call 613 941-2108 between 8:30 am and 4:30 pm or 613 941-3061 after regular office hours. The infectious diseases department must fill out the required SAP forms, which are usually available through the hospital pharmacy.

been used mostly in young children with underlying risk factors (e.g., chronic lung disease or immunodeficiency) or severe lung disease (e.g., hypercapnea or hypoxemia) requiring ventilatory support.

The intravenous route has been used in treatment for Lassa fever, hemorrhagic fever with renal syndrome, hantavirus infection<sup>4</sup> and severe adenovirus infection in immunocompromised children. The evidence for efficacy and safety with these uses is preliminary. The oral form of ribavirin, in conjunction with interferon  $\alpha$ , is effective in patients with hepatitis C.<sup>5</sup>

### Adverse effects

Administration of ribavirin as an aerosol is associated with nausea, headaches and, rarely, exacerbation or worsening of bronchospasm, both in infants and in care givers exposed to the drug. Ribavirin aerosol may cause rashes, conjunctivitis or opacities of contact lenses.

Systemic use of ribavirin (intravenous or oral administration) may cause dose-dependent anemia due to hemolysis and bone marrow suppression, both of which are reversible. Hemolytic anemia usually occurs after 10 days of therapy but may appear as early as 3 to 5 days after initiation of the drug; it is usually observed with doses of 1–2 g or higher.<sup>6</sup> Patients with preexisting cardiac disease in whom anemia develops are at increased risk of deterioration of cardiac status. In HIV patients receiving other nucleoside analogues (as part of highly active antiretroviral therapy), in addition to ribavirin, elevated concentrations of lactate and pyruvate have been reported; it has been postulated that these findings were secondary to mitochondrial toxic effects associated with both drugs.<sup>7</sup> In our own recent experience with SARS, we have seen hypocalcemia and hypomagnesemia associated with the use of high-dose ribavirin, and a recent report described an association between hypocalcemia even in patients who had been on lower doses of ribavirin as part of combination therapy for viral hepatitis.<sup>8</sup> In addition to these electrolyte disturbances (hypocalcemia and hypomagnesemia), hyperammonemia and pancreatitis have also been reported.<sup>9,10</sup> Central nervous system (CNS) effects, including CNS depression and mood changes, have been described; however, these effects are

usually seen only in patients receiving concurrent interferon treatment for hepatitis C,<sup>11</sup> which has been clearly associated with neuropsychiatric effects.

Box 3 lists patient groups in whom ribavirin should be avoided or modified, and Box 4 outlines appropriate monitoring for patients receiving ribavirin.

### Drug interactions

Case reports suggest that the effects of warfarin may be inhibited during treatment with ribavirin, and this inhibition may continue for up to 1 month after discontinuation of the ribavirin therapy.<sup>12</sup> Concurrent use of ribavirin and nucleoside analogue reverse-transcriptase inhibitors (e.g., zidovudine and stavudine) should be avoided because of the risk of lactic acidosis and other mitochondrial toxic effects, which may be higher in HIV patients who also have hepatitis C.

### Teratogenic potential

Because it is a nucleoside analogue, ribavirin interferes with DNA and RNA replication and hence may affect the embryo. Rodent studies have shown teratogenicity with relatively low doses (1–10 mg/kg) but not in nonhuman primates at doses of 60–120 mg/kg.<sup>13</sup> Pharmacokinetic modelling has suggested that aerosolized ribavirin may pose a teratogenic risk to health care workers.<sup>14</sup>

Although the true risk for teratogenic effects in humans is unknown, an industry-based registry at Schering Plough Inc. did not record a higher-than-expected teratogenic rate among several hundred pregnant patients with hepatitis C who were treated orally during their pregnancies.<sup>15</sup> There are no data on ribavirin exposure through breast-feeding. Clearly, the current experience with intravenous ribavirin in the treatment of SARS is likely to result in much higher

#### Box 2: Current recommendations for use of ribavirin in children with probable or suspected SARS

##### Intravenous

Loading dose 33 mg/kg IV, one time only (maximum 2 g/dose)

6 hours after loading dose, start IV doses of 16 mg/kg (maximum 1 g/dose) every 6 hours for 4 days

8 hours after the last dose of 16 mg/kg, start IV doses of 8 mg/kg (maximum 500 mg/dose) every 8 hours for 3 to 6 days, depending on the clinical course

##### Aerosol

20 mg/mL aerosol for 18 hours per day

OR

60 mg/mL aerosol for 2 hours of every 8 hours (i.e., 6 hours per day)

**Box 3: Patients for whom ribavirin use should be avoided or modified**

Pregnant women or women of child-bearing potential  
 Patients with a previous convincing history of hypersensitivity to ribavirin  
 Patients with comorbid illnesses such as hemoglobinopathy (e.g., thalassemia or sickle-cell anemia), unstable cardiac disease or gout (particular caution required)  
 Patients with renal insufficiency (see Box 1)

fetal exposure, and current recommendations include avoidance of the drug during pregnancy and lactation. Given the prolonged intracellular half-life and the current lack of knowledge in this regard, effective contraception should be practised by women who receive ribavirin, during treatment and for at least 6 months after treatment is completed. There are some concerns, as yet unproven, about potential effects on sperm; however, Schering's registry of almost 1000 men showed no malformations after exposure to the drug. Because ribavirin has been shown to be teratogenic only during embryogenesis (i.e., first trimester in humans), use of the drug in later stages of pregnancy may not increase the teratogenic risk.

If a woman needs ribavirin in pregnancy or has conceived within 6 months of her partner or herself being on the drug, she can be referred to the Motherisk Program at the Hospital for Sick Children (416 813-6780 or momrisk@sickkids.org) for counselling and follow-up.

**Efficacy of ribavirin in SARS**

Recent published reports from Hong Kong and Canada have shed light on early experience with ribavirin in combination with other antimicrobials, with or without steroids, in the treatment of SARS.

In Toronto, 7 patients were treated with oral oseltamivir, broad-spectrum antibiotics and intravenous ribavirin at 2 g loading dose, followed by 1 g every 6 hours for 4 days, then 500 mg every 8 hours for another 4 to 6 days.<sup>16</sup> This dosing regimen was based on a recently published dose schedule for hemorrhagic fever viruses. Of these 7 patients, 1 died, 1 showed improvement on mechanical ventilation, and the other 5 improved within 5 days. Of note, in addition to receiving antivirals and antimicrobials, the 5 patients who

improved had received earlier and more aggressive supportive care than the other 2 patients. These 5 have since recovered either completely (3 patients) or with mild dyspnea (2 patients) with 3 week follow-up. In contrast, of 3 patients who were treated only with broad-spectrum antibiotics, 2 died and 1 was still receiving ventilation in the intensive care unit at the time of writing (unpublished data). Since the publication of this case series<sup>16</sup> at the end of March, anecdotal reports have been received about a smaller number of patients who did not receive ribavirin and who have recovered without incident.

In Hong Kong, 10 patients were treated empirically with ribavirin: 9 intravenously at 8 mg/kg every 8 hours and 1 orally at 1.2 g every 8 hours.<sup>17</sup> Each patient received 1 of 2 corticosteroids, hydrocortisone or methylprednisolone. Treatment started 3 to 22 days (median 12.5 days) after the onset of symptoms. The authors reported resolution of fever and improvement in heart rate within 2 days of commencing treatment in 8 of the patients; the other 2 patients died of respiratory failure.

More data has further characterized the major outbreak of SARS in Hong Kong.<sup>18</sup> In 138 patients with suspected SARS, a combination of ribavirin and corticosteroids was given to patients if fever persisted for more than 48 hours and blood counts showed leukopenia, thrombocytopenia or both. As in the other Hong Kong study,<sup>17</sup> outcomes were not broken down according to which patients received ribavirin.

There are numerous methodological issues in these early reports that preclude any conclusions about the efficacy of ribavirin in the treatment of SARS. Given that the

**Box 4: Laboratory monitoring for patients who are receiving ribavirin**

Given what we currently know about the presentation of SARS and the side effects associated with high-dose intravenous ribavirin, the following laboratory monitoring is recommended:

Baseline glucose and electrolyte levels (especially serum calcium, magnesium and phosphorus), then daily monitoring tapering to monitoring as needed, as values stabilize

Baseline hemoglobin or hematocrit (or both), leukocyte count and platelet count, then daily monitoring while receiving ribavirin, followed by monitoring as needed until values stabilize

Baseline liver function tests and enzyme levels, including total bilirubin, alkaline phosphatase and lactate dehydrogenase, then daily monitoring if the baseline values are abnormal

Baseline creatinine kinase level, then daily monitoring along with urine monitoring if the baseline value is abnormal

Baseline serum amylase and serum lipase with twice-daily monitoring while receiving ribavirin

Baseline uric acid, then twice-weekly monitoring while receiving ribavirin

Baseline lactic acid, then twice weekly monitoring while receiving ribavirin or if anion gap is detected during routine blood work

putative causative agent is a new strain of coronavirus that has not previously affected humans, it will be critical to obtain more information on the in vitro susceptibility of this virus to ribavirin and other investigational and licensed antivirals. The US Food and Drug Administration has initiated such a screening program.

Until more information becomes available on the efficacy of ribavirin and the optimal management of SARS, it is likely that use will continue to be recommended at least in a subset of sicker patients. Canadian physicians should become familiar with the contradictions to ribavirin use and the established adverse effects of the drug and should closely monitor patients receiving ribavirin for as-yet-undescribed short-term and long-term adverse events.

From the Divisions of Clinical Pharmacology/Toxicology (Koren) and of Infectious Diseases (King), The Hospital for Sick Children, Toronto, Ont.; and the Divisions of Clinical Pharmacology (Knowles, Phillips), Infectious Diseases (Phillips) and Pharmacy (Knowles), Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Toronto, Ont.

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**Correspondence to:** Dr. Gideon Koren, Division of Clinical Pharmacology/Toxicology, The Hospital for Sick Children, 555 University Ave., Toronto ON M5G 1X8; fax 416 813-7562; [gkoren@sickkids.ca](mailto:gkoren@sickkids.ca)

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