

Acute and severe ribavirin-associated hyperuricemia and acute kidney injury: An underrecognized adverse effect

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Purpose. To report a case of ribavirin-associated severe hyperuricemia in an immunocompromised patient treated for respiratory syncytial virus (RSV) infection.

Summary. A 21-year-old male with a past medical history of B-cell acute lymphoblastic leukemia was in full remission after allogenic bone marrow transplantation complicated with chronic graft-versus-host disease. He was hospitalized due to fever, malaise, and respiratory syndromes. A diagnosis of RSV upper respiratory tract infection complicated by secondary pneumonia was made, and oral ribavirin (600 mg in 3 divided doses daily) and intravenous levofloxacin (750 mg once daily) were initiated. On day 2 of the hospital admission, the patient's uric acid levels had increased from a baseline of 4 to 6 mg/dL to values of 19.3 and 22.2 mg/dL after the fourth and fifth doses of ribavirin, respectively, and his serum creatinine steadily had increased from a baseline of 0.7 to 0.8 mg/dL to a value of 1.6 mg/dL. Ribavirin was discontinued after the sixth dose, and a single dose of intravenous rasburicase (7.5 mg) was administered. On day 3, the patient's serum uric and creatinine concentrations had decreased to 4.7 mg/dL and 1.1 mg/dL, respectively. He continued to recover on antibiotics and was discharged with normal uric acid and serum creatinine levels.

Conclusion. We report a case of severe hyperuricemia and acute kidney injury that developed early after initiation of ribavirin for RSV infection and suspected bacterial pneumonia in an immunocompromised patient without hepatitis C, requiring ribavirin discontinuation and rasburicase administration. To our knowledge, this is the first reported case of severe hyperuricemia in a patient treated with ribavirin for RSV infection rather than chronic hepatitis C. Clinicians should be aware of the possibility of acute and severe hyperuricemia following ribavirin administration.

Keywords:

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Medication use is an important cause of hyperuricemia.¹ While the exact incidence of drug-induced hyperuricemia is unknown, diuretics are probably the most common cause seen in clinical practice. Other medications commonly implicated include antitubercular drugs, low-dose aspirin, cytotoxic chemotherapy, calcineurin inhibitors, and nicotinic acid. Various mechanisms have been suggested, including increased uric acid reabsorption and/or decreased uric acid excretion in the renal tubuli, massive disruption of tumor cells (tumor lysis syndrome), and increased uric acid production.^{1,2} Drug-induced hyperuricemia is usually fully reversible upon discontinuation of the offending agent but may result in kidney injury and other manifestations of gout if not recognized and appropriately managed.^{1,3}

Hyperuricemia has been described as an adverse effect of ribavirin most commonly reported with use of the drug in combination with pegylated interferon- α 2a/b for the treatment of chronic hepatitis C. The precise culprit—whether it be ribavirin, interferon, a drug-disease interaction, or a combination thereof—and the mechanism of this adverse effect are unclear.⁴⁻⁹ Here we report a case of severe ribavirin-induced hyperuricemia associated with acute kidney injury in an immunocompromised patient treated for suspected respiratory syncytial virus (RSV) airway infection, requiring ribavirin discontinuation and rasburicase administration. To our knowledge, this is the first case report to describe severe ribavirin-associated hyperuricemia in a patient receiving ribavirin outside the context of chronic hepatitis C.

To gain further insights on this apparently underrecognized adverse effect of ribavirin, we conducted a systematic literature review using PubMed and adverse drug reaction databases. PubMed was searched for articles published from database inception until April 7, 2020, without language restrictions, using the search terms *ribavirin*,

hyperuricemia, uric acid, and urate nephropathy. We also conducted an advanced search using the MeSH term “ribavirin” in conjunction with “hyperuricemia,” “uric acid,” or “urate nephropathy.” Moreover, a random search using these terms was conducted. Additionally, we searched adverse drug reaction databases such as EudraVigilance (the European database of suspected adverse drug reaction reports), VigiAccess (the World Health Organization’s global pharmacovigilance database), and the Canada Vigilance Adverse Reaction online database using the terms *hyperuricemia, uric acid, and nephropathy*.

Case report

A year prior to admission to our institution for treatment of suspected RSV infection, a 21-year-old Arab male patient had undergone allogeneic bone marrow transplantation for Philadelphia chromosome–negative B-cell acute lymphoblastic leukemia and subsequently developed chronic graft-versus-host disease. Two and a half months prior to admission to our facility, he was in full molecular remission. On the day before his hospitalization, he had contacted his hematologist after developing fever and malaise, rhinorrhea, dry cough, and dyspnea and was referred for hospitalization.

On admission, the patient’s chronic oral medication regimen included cyclosporine (25 mg/d), prednisone (5 mg/d), voriconazole (600 mg/d), acyclovir (1,200 mg/d), sulfamethoxazole/trimethoprim (960 mg twice weekly), ursodeoxycholic acid (900 mg/d), ramipril (5 mg/d), bisoprolol (10 mg/d), esomeprazole (40 mg/d), calcium carbonate (600 mg/d), and vitamin D (800 units/d). His vital signs were normal. He was of normal body size (height, 178 cm; weight, 76 kg; body mass index, 24.0 kg/m²). His physical examination was unremarkable, and laboratory test results revealed macrocytic anemia (hemoglobin concentration, 11.1 g/dL) and a normal white blood cell count. A chest x-ray revealed

peribronchial cuffing but no infiltrates. A nasal swab for respiratory viruses tested positive for RSV via real-time polymerase chain reaction assay.

A diagnosis of RSV upper respiratory tract infection was made, and the immunocompromised patient was started on oral ribavirin (600 mg in 3 divided doses daily). On hospital day 2, he developed shortness of breath and pleuritic chest pain. His vital signs were notable for tachycardia (130 beats/min) and hypoxia (86% oxygen saturation when breathing room air). Computed tomography and angiography of the chest revealed bilateral perihilar infiltrations and left lower lobe consolidation compatible with lobar pneumonia, with no evidence of pulmonary emboli. He received oxygen supplementation via a high-flow nasal cannula, and intravenous levofloxacin (750 mg once daily) was started. Laboratory results revealed an increase in uric acid levels from baseline values of 4 to 6 mg/dL to values of 19.3 mg/dL after dose 4 and 22.2 mg/dL after dose 5 of ribavirin, and the serum creatinine concentration steadily increased from a baseline concentrations of 0.7 to 0.8 mg/dL to a value of 1.6 mg/dL. His hemoglobin concentration decreased from 11.1 g/dL to 10.3 g/dL. Ribavirin was discontinued after the sixth dose, and a single dose of intravenous rasburicase (7.5 mg) was administered after excluding glucose-6-phosphate dehydrogenase (G6PD) deficiency. On hospital day 2 the patient also developed moderate leukopenia (white blood cell count, 1,600-2,000 cells/ μ L; neutrophil count, 970-1,140 cells/ μ L). Later during the day, his blood pressure decreased temporarily from 110/70 to 95/50 mmHg but quickly rebounded with fluid therapy. Levofloxacin was discontinued, and vancomycin and piperacillin/tazobactam were initiated. Bronchoscopy was deferred due to impending respiratory failure.

On hospital day 3, the patient's condition improved significantly. His hypoxia resolved with only minimal oxygen supplementation. His serum uric acid concentration

decreased to 4.7 mg/dL, his serum creatinine concentration decreased to 1.1 mg/dL, and both values continued to improve on the following day (uric acid, 3.5 mg/dL; creatinine, 0.8 mg/dL) and remained stable during the rest of the hospitalization. The patient continued to quickly recover with antibiotic therapy, and therefore resumption of RSV-directed therapy was considered unnecessary. He was discharged 9 days after admission with normal uric acid and serum creatinine levels.

Discussion

Drug-induced hyperuricemia and its potential clinical sequelae (eg, gout, kidney injury) collectively constitute an adverse drug effect that is often overlooked in clinical practice. While in most patients the magnitude of drug-induced hyperuricemia is mild and of limited clinical consequence, there is great variability in treatment response and some patients develop significant uric acid increases associated with acute or chronic uric acid nephropathy, nephrolithiasis, and gout. Mechanisms of drug-induced hyperuricemia include uric acid overproduction and/or a reduction in renal uric acid excretion.^{1,2}

Use of thiazides and loop diuretics is one of the most common causes of secondary hyperuricemia. They decrease renal uric acid clearance by reducing tubular secretion and increasing reabsorption.^{1,2} Diuretic-induced hyperuricemia appears to be dose dependent, manifests within a few days of treatment initiation, and persists during continued administration.¹⁰ The median increase of uric acid is small (about 1.0 mg/dL with use of thiazide diuretics),¹¹ but increases may range from 6% to 35% of baseline values.^{3,12} Diuretic-induced hyperuricemia is reversible after discontinuation of the offending agent.^{1,3,12}

All reported cases of ribavirin-associated hyperuricemia occurred in patients with hepatitis C receiving combination therapy with other antiviral agents, most commonly pegylated interferon- α 2 (with or without telaprevir) and sofosbuvir.^{4-9,13,14} Significant hyperuricemia associated with use of ribavirin in combination with pegylated interferon- α 2 has been described in a number of case reports, case series, and cohort studies (summarized in Table 1). In a case series reported by Yamashita et al,⁵ among 50 patients use of pegylated interferon- α 2b plus ribavirin was associated with a mild but statistically significant rise in the mean (SD) uric acid concentration, from 5.4 (1.2) mg/dL at baseline to 5.8 (1.6) mg/dL during combination therapy ($P = 0.0023$ for paired comparison), and the concentrations remained within the normal range in 85% of the patients. Interestingly, urinary uric acid excretion was increased after initiation of combination therapy with ribavirin and pegylated interferon- α 2b, suggesting increased uric acid synthesis rather than reduced renal excretion as the mechanism of hyperuricemia. Moreover, the rise in uric acid was not associated with markers of hemolysis (a rise in lactate dehydrogenase [LDH] or a decline in hemoglobin), suggesting that other mechanisms contributed to ribavirin-induced hyperuricemia.

Our patient developed severe hyperuricemia and acute kidney injury within 24 hours after the initiation of ribavirin monotherapy. The early onset and the magnitude of the uric acid elevation were different from those observed with use of diuretics^{1,12} or in most patients treated with ribavirin and interferon combination therapy, but a case of early-onset hyperuricemia of a similar magnitude was previously described in association with ribavirin and pegylated interferon combination therapy.⁸

The probability of a causal relationship between ribavirin therapy and hyperuricemia in our patient is high. Using the validated adverse drug reaction probability scale of Naranjo

et al,¹⁵ we determined that causality between ribavirin use and development of severe hyperuricemia can be considered probable (a cumulative score of 7) on account of previous reports of this reaction (+1), timing (+2), improvement after drug discontinuation (+1), the lack of an alternative explanation (+2), and the objective assessment of the adverse event (+1). The patient had no history of hyperuricemia, his electronic medical record revealed normal uric acid levels in recent laboratory examinations, and he had no chronic disease predisposing to hyperuricemia, such as obesity, impaired glucose tolerance and/or insulin resistance, alcohol abuse, or renal disease. The rapid and extreme rise in uric acid levels and rapid reversal after the administration of rasburicase and discontinuation of ribavirin strengthen a causal association. There was no reasonable alternative explanation for the extreme rise in uric acid. Cyclosporine use is associated with hyperuricemia in 30% to 85% of renal transplant recipients, probably occurring through an increase in proximal tubule uric acid reabsorption and a reduction in glomerular filtration rate secondary to afferent arteriolar vasoconstriction.¹ However, cyclosporine-induced hyperuricemia was unlikely in the case reported here, as the patient had normal uric acid levels for months while on a long-term cyclosporine regimen and cyclosporine trough levels were in the low-normal range (84 ng/mL) during a hospitalization about 1 year previously.

Approximately 30% of uric acid is eliminated via the biliary and gastrointestinal tract and the remaining 70% through the kidneys; thus, acute kidney injury may induce hyperuricemia.¹⁶ However, this is an unlikely explanation for development of hyperuricemia in our patient, since (1) he had developed acute kidney injury previously without a significant elevation in uric acid levels; and (2) his mild acute kidney injury was unlikely to have increased uric acid concentrations to the magnitude observed. Thus, while reasons for the acute kidney injury were most likely multifactorial, including sepsis and acute uric acid

nephropathy, it is unlikely that the extreme rise in uric acid levels can be fully explained by acute kidney injury.

The underlying mechanism of ribavirin-associated hyperuricemia is unclear. One of the proposed mechanisms is the induction of dose-dependent hemolytic anemia.^{6,17}

Ribavirin is transported into erythrocytes by the nucleoside transporter and is converted into ribavirin mono-, di-, and triphosphate derivatives. These ribavirin phosphates accumulate intracellularly because erythrocytes lack the phosphatase needed to hydrolyze them, resulting in cellular toxicity and subsequent hemolysis.¹⁸ In our patient, there was a mild decline in hemoglobin (about 1 g/dL) on the day of the marked increase in uric acid, 2 days after initiation of ribavirin, but no concomitant increase in indirect bilirubin, LDH, or aspartate transaminase. We therefore believe that hemolysis cannot fully explain the patient's hyperuricemia. Moreover, the occurrence of ribavirin-associated hyperuricemia in the absence of significant hemolysis has been described in the literature, suggesting that additional mechanisms may exist.

Ribavirin, a guanosine analogue, inhibits inosine monophosphate dehydrogenase (IMPDH), the key enzyme in the de novo synthesis pathway of guanosine triphosphate (GTP) from inosine monophosphate. GTP is required for viral replication. Inhibition of the IMPDH pathway by ribavirin may result in the increased transformation of IMP to hypoxanthine and xanthine, precursors of uric acid. Thus, ribavirin could directly increase serum uric acid synthesis through the hypoxanthine/xanthine pathway.^{18,19} Interestingly, hyperuricemia is also a common adverse effect of mizoribine,²⁰⁻²² an immunosuppressive drug and competitive inhibitor of IMPDH²³ with structural similarity to ribavirin. In fact, severe hyperuricemia (a rise in the uric acid concentration of 10.7-21.2 mg/dL) has been reported after mizoribine monotherapy.²⁰

We do not know why the rise in uric acid was so extreme in our patient. We hypothesize that he could carry genetic polymorphisms in genes affecting the pharmacokinetic or pharmacodynamic pathways of ribavirin. Single nucleotide polymorphisms in candidate genes thought to be involved in ribavirin pharmacokinetics have been associated with high plasma ribavirin trough concentrations.^{24,25} Similarly, hypofunctional polymorphisms in the genes encoding IMPDH have been described.²⁶ Thus, it is possible that genetic variants in these pathways, while not associated with hyperuricemia at baseline, could lead to an extreme rise in uric acid when ribavirin blocks compensatory mechanisms, thereby explaining the extreme response in our patient.

If resumption of RSV-directed therapy had been required in our patient, in view of the severe adverse event related with probable causality to oral ribavirin use, we believe that a rechallenge with oral ribavirin would not have been adequate. However, we would have considered administering aerosolized ribavirin by inhalation, which has been reported to result in 500- to 1,000-fold higher peak concentrations in respiratory secretions versus plasma.²⁷ Assuming that ribavirin-associated hyperuricemia is exposure dependent, we therefore believe that a rechallenge with aerosolized ribavirin would have been feasible. Alternatively, other RSV-directed therapies, such as palivizumab or intravenous immune globulin, could have been considered.

Conclusion

To the best of our knowledge, this is the first reported case of severe hyperuricemia appearing early after initiation of ribavirin in a patient without hepatitis C being treated for RSV infection. The acute and severe hyperuricemia was associated with acute kidney injury

and required ribavirin discontinuation and rasburicase administration. Clinicians should be aware of the possibility of acute and severe hyperuricemia shortly after ribavirin initiation.

Disclosures

The authors have declared no potential conflicts of interest.

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Figure 1. The patient's serum uric acid and creatinine concentrations before and after the initiation and discontinuation of ribavirin therapy and administration of rasburicase.

Key Points

- Ribavirin and interferon combination therapy in patients with hepatitis C has been associated with mild increases in uric acid, and the relative contribution of each medication is unclear.
- An immunocompromised patient treated with oral ribavirin for respiratory syncytial virus infection developed a rapid-onset and extreme increase in serum uric acid concentrations associated with acute kidney injury requiring rasburicase administration.
- Clinicians should be aware of this rare adverse effect, which may also occur during ribavirin monotherapy in patients without hepatitis C.

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Table 1. Summary of Evidence on Ribavirin-Associated Hyperuricemia From Literature Review

Authors (Year Published)	Study Design	Antiviral Medications	Oral Ribavirin Daily Dose, mg/d	Serum Uric Acid (Baseline/Max), mg/dL	Time to Max Uric Acid Level	Main Findings	Intervention
Kumada et al ¹⁴	Randomized control trial (<i>n</i> = 60)	Group A: telaprevir + IFN β + ribavirin Group B: IFN β + ribavirin	Weight-based dosing ^a	Not stated	Not stated	20.5% of patients in group A had hyperuricemia vs 3.3 % in group B	None
Davis et al (1998) ⁶	Randomized control trial (<i>n</i> = 173)	Peg-IFN α 2b + ribavirin	1,000-1,200	Not stated	Not stated	42 of 173 patients (24%) had high serum uric acid levels	None
Sangrador Pelluz et al (2013) ⁹	Retrospective observational (<i>n</i> = 88)	Peg-IFN α 2b + ribavirin + telaprevir	Not stated	Not stated	Median (IQR), 57 (16-82) days	50% of patients had hyperuricemia	None
Moreno-Monteagudo et al (1998) ⁷	Prospective cohort (<i>n</i> = 60)	Peg-IFN α 2b + ribavirin	1,000-1,200	Not stated	Within 1st month	5 of 60 patients (8.3%) had hyperuricemia	None
Sato et al (2018) ¹³	Prospective cohort (<i>n</i> = 142, 50 with uric acid data)	Sofobuvir + ribavirin	Weight-based dosing ^a	Median, 5.6/7.5	Within 1st week	8 of 50 patients (16%) presented with hyperuricemia	6% of patients received febuxostat
Yamashita et al (2008) ⁵	Case series (<i>n</i> = 50)	Peg-IFN α 2b with or without ribavirin	100-800	Mean (SD), 5.4 (1.2)/5.8 (1.6)	Not stated	Mild but statistically significant rise in uric acid	None
Knorr et al (2015) ⁸	Case report	Peg-IFN α 2b + ribavirin	400	Not stated/23.4	72 hours	Severe hyperuricemia and urate nephropathy	Discontinuation of ribavirin and Peg-IFN α 2b,

Fonatana et al (2001) ⁴	Case report	Peg-IFN α 2b + ribavirin	1,200	Mean, 6.8/9.6	Week 18	Uric acid nephrolithiasis and hyperuricemia ascribed to ribavirin-induced hemolysis	treatment with rasburicase and hemodialysis Discontinuation of ribavirin, initiation of allopurinol
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Abbreviations: IQR, interquartile range; max, maximum; Peg-IFN, pegylated interferon; SD, standard deviation

^aWeight-based dosing was as follows: weight of ≤ 60 kg, 600 mg/d; weight of >60 kg to 80 kg, 800 mg/d; weight of >80 kg, 1,000 mg/d.

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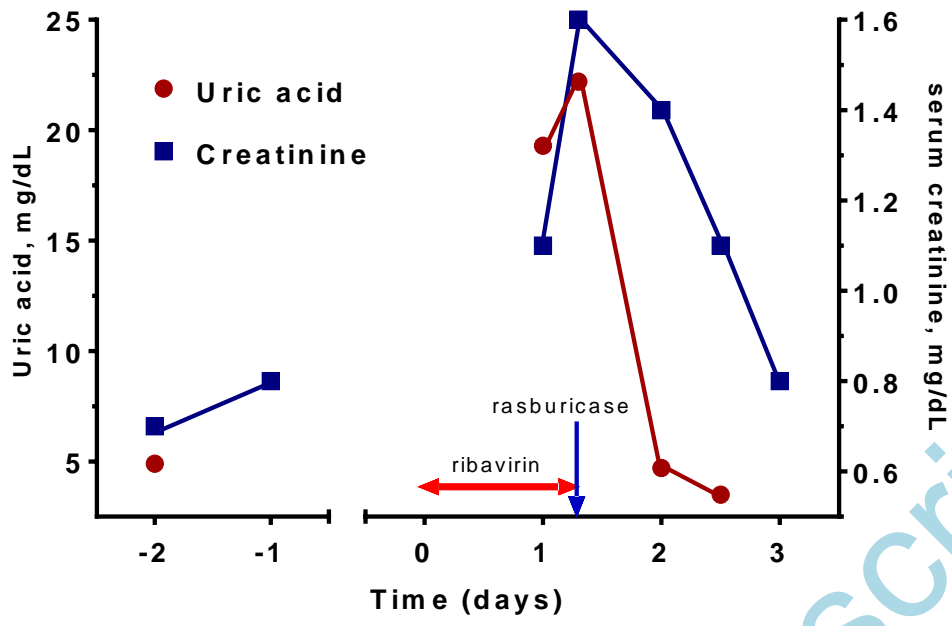


Figure 1