

# A Case Series on Suspected Remdesivir Induced Hyperammonemia

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## ABSTRACT

Remdesivir is a broad spectrum anti-viral drug that has shown to inhibit SARS-CoV-2. In absence of any effective treatment for SARS-CoV-2 infection (COVID-19), Remdesivir has been tried for a compassionate use in severe COVID-19. Remdesivir has shown promise in the management of patients with COVID-19 although recent studies have shown concerns with its effectiveness and safety in practice. Despite this there is a need to document potential Adverse drug Reaction (ADR) to guide future decisions. We describe 2 cases of Suspected Remdesivir-induced hyperammonemia (SRIH) in patients with normal liver function. Serum ammonia levels was raised much above the baseline after a fortnight of therapy. After completion of the therapy, there was gradual improvement and normalization of serum ammonia levels. This suggested a causal relationship which was possibly due to the administration of Remdesivir drug. With the increasing use, physicians should be aware of this potential ADR of Remdesivir and evaluate ammonia levels in patients taking Remdesivir who present with alterations in mental status.

**Keywords:** Adverse drug reaction, COVID-19, Hyperammonemia, Remdesivir, SARS-CoV-2.

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## I. INTRODUCTION

Remdesivir is an adenosine analogue that has a broad-spectrum antiviral activity against several viruses such as respiratory syncytial virus, Nipah virus, Ebola virus (EBOV), Middle East respiratory syndrome (MERS-CoV), and Severe Acute respiratory Syndrome Coronavirus-1 (SARS-CoV-1) [1]-[3]. In current pandemic situation increasing use of Remdesivir for treating moderate to severe novel coronavirus disease 2019 (COVID-19).

The primary mechanism of Remdesivir is the incorporation of the nucleoside triphosphate GS-443902 into nascent RNA chains by viral RNA-dependent RNA polymerase, causing delayed RNA chain termination during the process of viral replication [4]. In summary, Remdesivir is a prodrug and inhibits viral RNA polymerases and decreases viral RNA production when intracellularly metabolized to an ATP analogue, this results in the termination of RNA transcription and decreases viral RNA production [4].

It is important to continue to collect safety data on the repurposed use of Remdesivir for the treatment of patients with COVID-19 alongside the collection of additional data regarding its effectiveness in patients with moderate to severe disease.

The common adverse events noted during compassionate use of Remdesivir in patients with COVID-19 are rash, diarrhea, hypotension, abnormal liver function, increase

serum aminotransferase and renal impairment [5]. Suspected Remdesivir-induced hyperammonemia (SRIH) is serious adverse drug reaction which is not well documented in literature.

Here we present two case reports of SRIH both occurring in patients with no history of underlying liver disease and its normalization when treatment was completed.

These case reports of nonhepatic hyperammonemia, i.e., elevated serum ammonia secondary to a nonhepatic etiology have been rarely reported for Remdesivir. This information can further guide physicians and others, for its use as well as safety of patients in management of COVID-19.

## II. OBSERVATIONS

### A. Case 1

An 80 years old hypertensive and hypothyroid male patient was brought to Emergency Medicine Department of tertiary care hospital with complains of cough for 4 days which was dry in nature, weakness for 2 days, low grade fever for 2 days and breathing difficulty for 1 day. No past history of Tuberculosis, COPD, Asthma, IHD, CKD and no surgical past history. Patient was diagnosed with COVID-19 Pneumonitis.

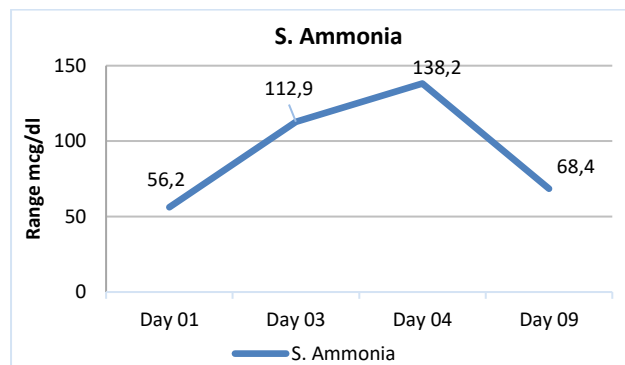


Fig. 1. Elevations in S. Ammonia after Remdesivir therapy and fall after completion of therapy.

On admission the patient was conscious and oriented, Temperature was 99.6 F, BP-150/80 mmHg, RR-30/min, pulse-80/min and SPO2-98% on non-rebreather mask 06 L/min Oxygen flow. The patient tested positive for COVID-19 by Rapid antigen testing and RTPCR.

Her investigations on the day of admission were as follows: Hb: 12.2 g/dl, WBC: 6550 cells/cumm, platelets: 1,50,000 cells/cumm, **Creatinine: 1.48 mg/dL**, Urea: 43.7 mg/dl, SGPT: 36 U/L, SGOT: 76 U/L, ALP: 31 U/L, Total Bilirubin :0.22 mg/dl, A/G Ratio: 2.57 % and inflammatory markers like **D-dimer: 4.47 µg/ml (<0.5)**, **ESR: 02 mm/hr.**, **IL-6: 46.1 Pg/ml** and **CRP: 65.49 mg/L (<5.0)**.

She was treated with Injection Remdesivir 200 mg IV on day of admission then given maintenance dose of 100 mg IV for 5 days. Other treatment included Injection Piperacillin 2.25 gm IV thrice a day, Injection Metronidazole 100 CC IV thrice a day, Injection Ceftriaxone 2 gm IV once a day, Injection Pantoprazole 40 mg IV once a day, Injection Metoclopramide 1 Ampule IV twice a day, Injection LMWH 0.6 CC SC twice a day, Injection Methylprednisolone 80 mg IV once a day, Tablet Azithromycin 500 mg Once a day, Tablet Rifaximin 550 mg twice a day, Tablet Vitamin-C 500 mg twice a day and given other supportive treatment.

On day 3, Laboratory Investigation showed Patient's serum ammonia level was raised to 112.9 mcg/dl at the time of 3<sup>rd</sup> dose of Injection Remdesivir. On day 4 again serum ammonia level was raised to 138.2 mcg/dl at the time of 4<sup>th</sup> dose of Injection Remdesivir. All possible causes were ruled out. Treatment was completed on day 5, Remdesivir was suspected for Hyperammonemia. On day 9<sup>th</sup> Repeated serum ammonia level which was lesser than the base line. Despite Remdesivir and steroid therapy, this patient succumbed to COVID-19 pneumonia on day 13<sup>th</sup> of admission.

### B. Case II

A 64 years old hypertensive and diabetic female patient was brought to Emergency Medicine Department of tertiary care hospital with complain of breathing difficulty for 5 days, dry cough for 4 days, fever for 3 days, and loss of appetite for 2 days. No past history of Tuberculosis, COPD, Asthma, IHD, CKD and no surgical past history. Patient was diagnosed with Covid 19 Pneumonitis.

On admission the patient was conscious and oriented, Temperature was 98.6 F, BP-130/70 mmHg, RR-28/min, pulse-98/min and SPO2-94% on non-rebreather mask 15 L/min Oxygen flow. The patient tested positive for COVID-19 by Rapid antigen testing and RTPCR.

Her investigations on the day of admission were as follows: Hb: 13 g/dl, WBC: 8300 cells/cumm, platelets: 3,14,000 cells/cumm, Creatinine: 0.70 mg/dL, Urea:52.3 mg/dl, SGPT: 16 U/L, SGOT: 29 U/L, ALP: 100 U/L, Total Bilirubin :0.70 mg/dl, A/G Ratio: 1.38 % and inflammatory markers like **D-dimer:2.08 µg/ml (<0.5)**, **ESR: 120 mm/hr.**, **IL-6: 197.9 Pg/ml** and **CRP:348.83 mg/L (<5.0)**.

She was treated with Injection Remdesivir 200 mg IV on day of admission then given maintenance dose of 100 mg IV for 5 days. Other treatments included, Injection Meropenem 2 gm IV thrice a day, Injection Levofloxacin 750 mg IV once a day, Injection Pantoprazole 40 mg IV twice a day, Injection Ondansetron 4 mg IV thrice a day, Injection Heparin 25000 IU IV Infusion, Injection Lantus 14 Units SC twice a day, Tablet Aspirin 75 Once a day, Tablet Metoprolol 25 mg twice a day, Tablet Vitamin-C 500 mg thrice a day, Injection Tocilizumab 400 mg IV was given after 1<sup>st</sup> day of admission, Injection Dexamethasone 8 mg IV thrice a day was given after 4<sup>th</sup> day of admission.

On day 4 patient developed mild Neurological symptoms. On day 5, Laboratory Investigation showed Patient's serum ammonia level was raised. Treatment was completed on day 5. Drug Injection Remdesivir was suspected for Hyperammonemia.

On day 13<sup>th</sup> Repeated serum ammonia level which was lesser than the base line. Patient was discharged with stable condition on day 15<sup>th</sup>.

### III. DISCUSSION

Remdesivir is an anti-viral agent that has shown a significant inhibitory effect in vivo and in vitro studies against SARS-CoV-2 and appears to be ahead of other repurposed drugs being tried for the treatment of COVID-19 [5]. FDA and European Medicines Agency (EMA) has currently authorized Remdesivir only in severe COVID-19 infection in both adults and children [5]. The safety profile of Remdesivir in COVID-19 is incompletely characterized in COVID-19 While the safety data from the previous use during acute Ebola Virus Disease (EVD) suggest no specific alarm, COVID-19 differs profoundly in its clinical characteristics from EVD. Nevertheless, hitherto no safety findings allow Remdesivir to be used in COVID-19, under a proper pharmacovigilance [5]. Special attention should be given for disproportionate rise in ALT or decrease in GFR, during the treatment with Remdesivir [5].

Remdesivir has an elimination half-life of 1 hour following a single 30-minute intravenous infusion. Under the same conditions, the elimination half-lives of the Remdesivir metabolites GS-441524 and GS-704277 are 27 hours and 1.3 hours, respectively [6]. The nucleoside triphosphate metabolite has a half-life of 14h in non-human primates. The nucleoside triphosphate metabolite has a half-life of approximately 20 hours in humans [6].

These cases have raised concerns regarding SRIH in patients with COVID-19. Hyperammonemia is life-threatening condition which can affect patients at any age [7]. Elevations of ammonia in plasma indicate its increased production and/or decreased detoxification [7]. The hepatic urea cycle is the main pathway to detoxify ammonia; it can

be defective due to an inherited enzyme deficiency or secondary to accumulated toxic metabolites or substrate depletion [7]. A variety of environmental causes and medications may also lead to ammonia toxicity [8].

In these two case reports, COVID-19 patients developed hyperammonemia during Remdesivir treatment. Laboratory finding suggested that sudden rise in serum ammonia level on 5<sup>th</sup> day in patient 1, 4<sup>th</sup> day in patient 2 during course of admission which returned to base line after treatment was completed. Causal relationship between drug and event suggested that it was possibly due to the administration of Remdesivir drug.

Overall, there is a need to continually monitor ADR arising from Remdesivir to provide future guidance. There is a role for Drug and Therapeutic Committees (DTCs) in hospitals to enhance ADR reporting as well as continue to promote evidence-based medicine (EBM) to optimize treatment for patients with COVID-19 and other diseases [9]. Solidarity Trial of WHO found that treatment of Remdesivir had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients [10]. This demand updating physicians on the effectiveness and safety of Remdesivir as new information becomes available in line with activities and recommendations for managing the entry of new medicines into clinical care [9]. physicians should be aware of this possible association and perform serum ammonia level monitoring when prescribing Remdesivir.

#### IV. CONCLUSION

The use of the novel antiviral Remdesivir in the treatment of COVID-19 pneumonia may put patients at risk of SRIH. In presented two cases, the Hyperammonemia resolved by the time therapy was completed. More data on the safety of Remdesivir is needed especially when our country is anticipating a third wave of the pandemic.

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