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The effect of remdesivir on heart in pregnant female rats

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Abstract: Remdesivir is the first medication that the FDA has authorized for use in treating COVID-19 pandemic. To evaluate the effect of remdesivir on level of sodium and potassium in blood and its effect on heart tissue in pregnant female rats. 10 pregnant female rats were used and split into two groups. 1ST group was a control group that was treated with distilled water every 48 hours, starting from 5th day of pregnancy until 19th day. 2nd group was treated with remdesivir at a concentration of 5 mg/kg body weight, every 48 hours, beginning on the 5th day of pregnancy and ending on the 19th day. On day 20, the animals were sacrificed and blood samples were taken to conduct the required tests, then an autopsy was performed to remove heart and make histological sections. Giving remdesivir was administered to the 2nd group, the blood serum potassium level significantly decreased and the sodium level significantly increased , additionally, blood congestion and hemorrhage occurred, some blood cells lysed, and there were severe cases of inflammatory cell infiltration in the heart sections compared to the 1st group. The use of remdesivir caused an imbalance in the level of electrolytes in blood and tissue damage to the heart muscle.

Keywords: *Heart, Potassium, Pregnant, Remdesivir, Sodium.*

1. Introduction

Beginning in Wuhan, China's seventh most populated city, Sever Acute Respiratory Syndrome-Coronaviruse-2 (SARS-CoV-2) was identified by the World Health Organization (WHO) in December 31, 2019 as a currently unknown pandemic [1]. On January 7, 2020, the novel coronavirus was discovered to be the cause [2]. On February 11, 2020, the virus responsible for the new cases was named SARS-CoV-2, after which WHO and International Committee on Taxonomy of Viruses, respectively, declared that COVID-19 was the coronavirus disease of 2019 [3].

The occurrence of pregnancy during the period of infection with Covid-19 leads to an exacerbation of the disease, and the infection becomes more severe as the period of birth approaches [4]. Although they are mostly meant to treat other illnesses, a number of antiviral medications have been used, repurposed, and are being researched for COVID-19. These medications may be able to stop the virus from replicating, lower morbidity, and alleviate symptoms for individuals with COVID-19 [5]. The first emergency medication authorized by the US Food and Drug Administration (FDA) to treat COVID-19 was remdesivir [6]. Its chemical formula is $C_{27}H_{35}N_6O_8P$, it is an adenosine monophosphoramidate analogue prodrug that was created in reaction to the West African Ebola outbreak . It inhibits viral RNA synthesis by suppressing RNA-polymerase and postponing chain termination due to competition with endogenous adenosine triphosphate, which prevents virus replication[7]. Among the most important side effects of using this drug is an increase in level of transaminase, urea, and creatinine [8].

Because the lack of data on effects of remdesivir on heart, the aim of this research is to ascertain the impact of this drug on levels of sodium and potassium in blood and on the heart tissue of pregnant females.

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2. Materials and Method

We used (10) female white Sprague-Dawley rats, acquired from Tikrit University's College of Veterinary Medicine's animal house, at the age of (12-14) weeks, with weights ranging from (200-250) grams, and in good health. The females were housed in cages with males of the same breed, one male for every two females during the night. Since the vaginal plug or the presence of sperm in the vaginal fluid is proof of the insemination process, the female were inspected the following morning. Female are deemed pregnant on day zero [9]. The females were divided into two groups:

1. Control group: distilled water was given every 48 hours starting from day 5 to day 19 of pregnancy.

2. Remdesivir-treated group: Remdesivir was given via subcutaneous injection at a concentration of (5 mg/kg body weight), according to the dose recommended by Ping Du *et al* (2021)[10], every 48 hours starting from day 5th to day 19th of pregnancy.

The pregnant rats fasted for 12 hours, then were anesthetized, and 3-4 ml of blood was Pulled from the heart and put in anticoagulant-free test gel tubes for the purpose of obtaining serum using a centrifuge at a speed of 3000 rpm and using a micropipette. It was distributed serum was obtained in four parts using Eppendorf tubes in order to avoid repeated thawing and freezing of the sample. The temperature at which the samples were stored was -20°C for the purpose of conducting the required tests, after which the abdomen of the pregnant rats was incised using a dissection kit and the heart was obtained for the purpose of making histological sections according to (Bancroft and Cook .,1998) [11].

The concentration of sodium and potassium was identified using spectrophotometry, as specified in the Randox biochemical kit by (Tietz et al., 1986)[12]. Duncan's multiple ranges test, the Analysis of Variance test, and a significance level of P≤ 0.05 were used to statistically analyze the results .

3. Result and Discussion

3.1. Biochemical Parameters

Table 1 illustrates that 2nd group of pregnant female rats treated with remdesivir had a significant increase (P≤0.05) in level of sodium in blood serum, while level of potassium in the blood serum decreased significantly compared to 1st group.

Table 1.
Biochemical parameters.

Parameters / groups	Na +2 (mg/dl)	K +2 (mg/dl)
Control Group	105.3057± 1.48469 b	4.8171± 0.0363 a
Remdesivir Groupe	123.1171± 2.93555 a	1.2557± 1.08056 b

Note: *Arithmetic mean ± standard error is represented by the values. At a significance level (P < 0.05), different letters indicate a significant difference. There are five animals in each group.

The major roles of electrolytes like sodium and potassium in mammals are to maintain water distribution and osmotic pressure. As cofactors for enzymes, these ions are crucial for oxidation-reduction reactions, heart muscle function, and pH maintenance[13].

A significant increase in level of sodium in 2nd group compared to the 1st group is consistent with what was indicated (Veklury.,2024)[14] ,One of the most common metabolic adverse events reported after using remdesivir is increased sodium or high blood sodium by (3%). Eight patients suffered elevated blood pressure and six patients got atrial fibrillation in the first compassionate use trial of remdesivir, which was used to treat 53 individuals infected with COVID-19[15]. Remdesivir injections' inactive ingredients, which comprise the sodium salt sulfobutylether-β-cyclodextrin (SBECD) and water, or which may also include sodium hydroxide or hydrochloric acid to modify the pH, could be the cause of the elevated sodium level[16].

As for potassium and its low level in blood serum after using the drug remdesivir, it appears that the distribution of potassium across the cell membrane is crucial for normal cellular function [17]. Potassium

plays a significant part in regulating heart rhythm and muscle function. In addition to sodium, potassium also plays a role in controlling the blood's and tissues' acid-base and water balance [18].

The primary counterregulatory mechanism of the main axis of the renin-angiotensin system (RAS), which is crucial for controlling blood pressure and electrolyte balance by balancing sodium and potassium, is the level of potassium in blood plasma and its relationship to angiotensin-converting enzyme 2 (ACE2) [19].

Microscopic examination of histological sections of the heart of pregnant female rats in the 1st group showed normal shape and arrangement of parallel, normal cardiac muscle cells, Figure 1. As for the heart in 2nd group of pregnant female rats treated with remdesivir, the prepared histological sections showed the occurrence of congestion and hemorrhage with lysis of some blood cells and acute infiltration of inflammatory cells occurs, Figures (2-4).

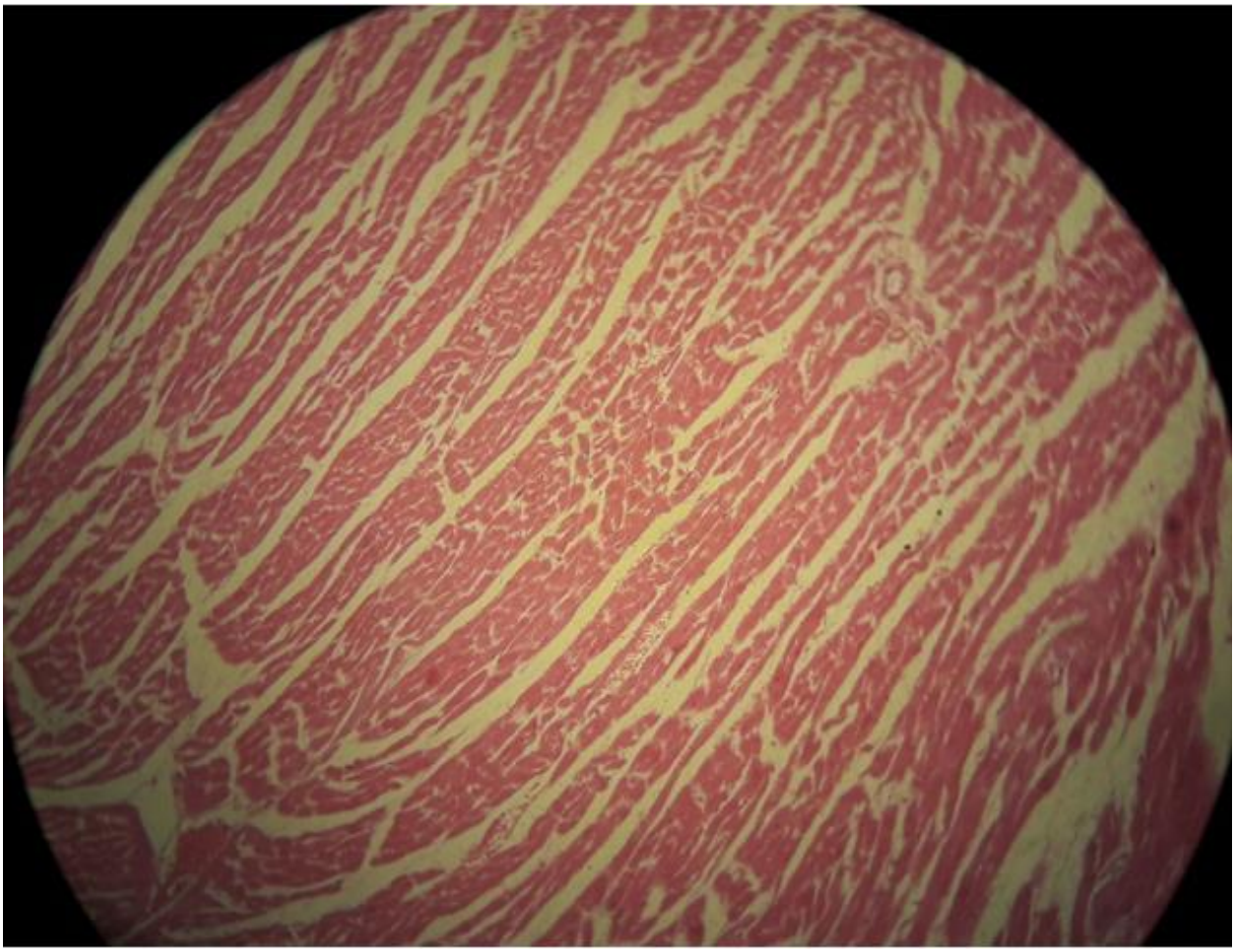

Figure 1.
Histological section of the heart of a pregnant female rat from control group showing parallel cardiac muscle cells. H&E stain: 100 X.

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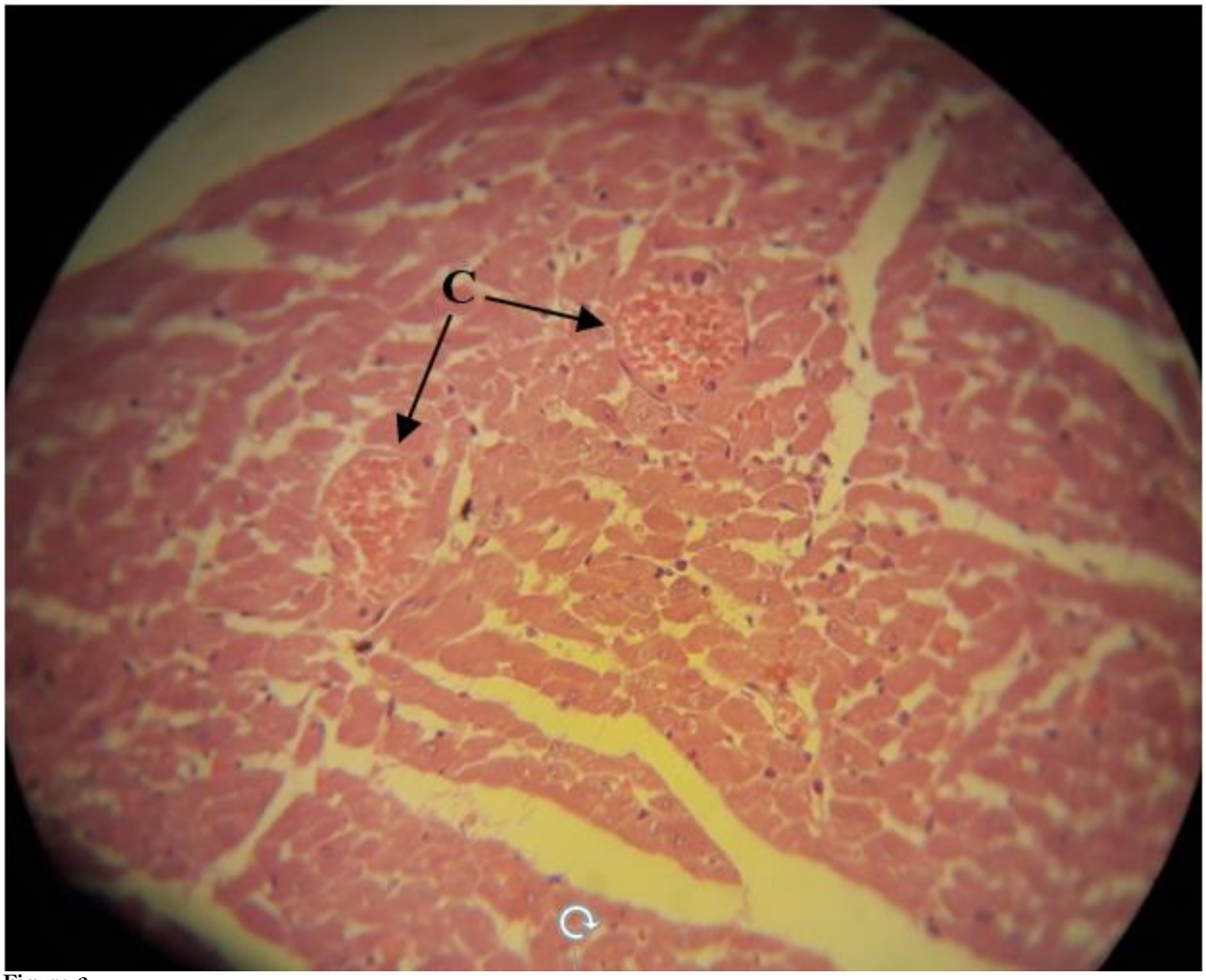

Figure 2.
Histological section of the heart of a pregnant female rat from 2nd group showing congestion (C). H&E stain: 400X.

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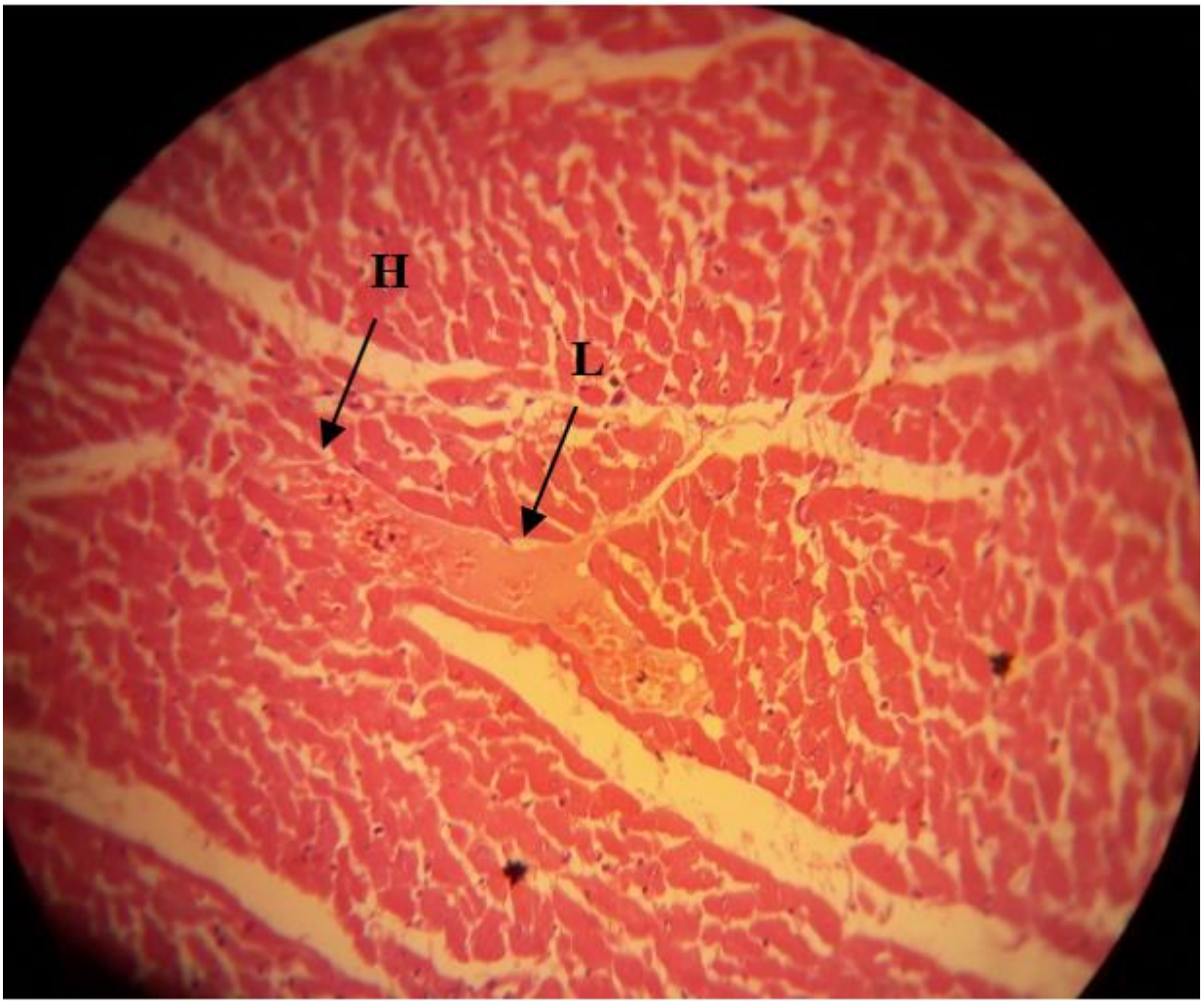

Figure 3.
Histological section of the heart of a pregnant female rat from 2nd group showing Hemorrhage(H) and lysis (L)of some blood cells. H&E stain: 400X.

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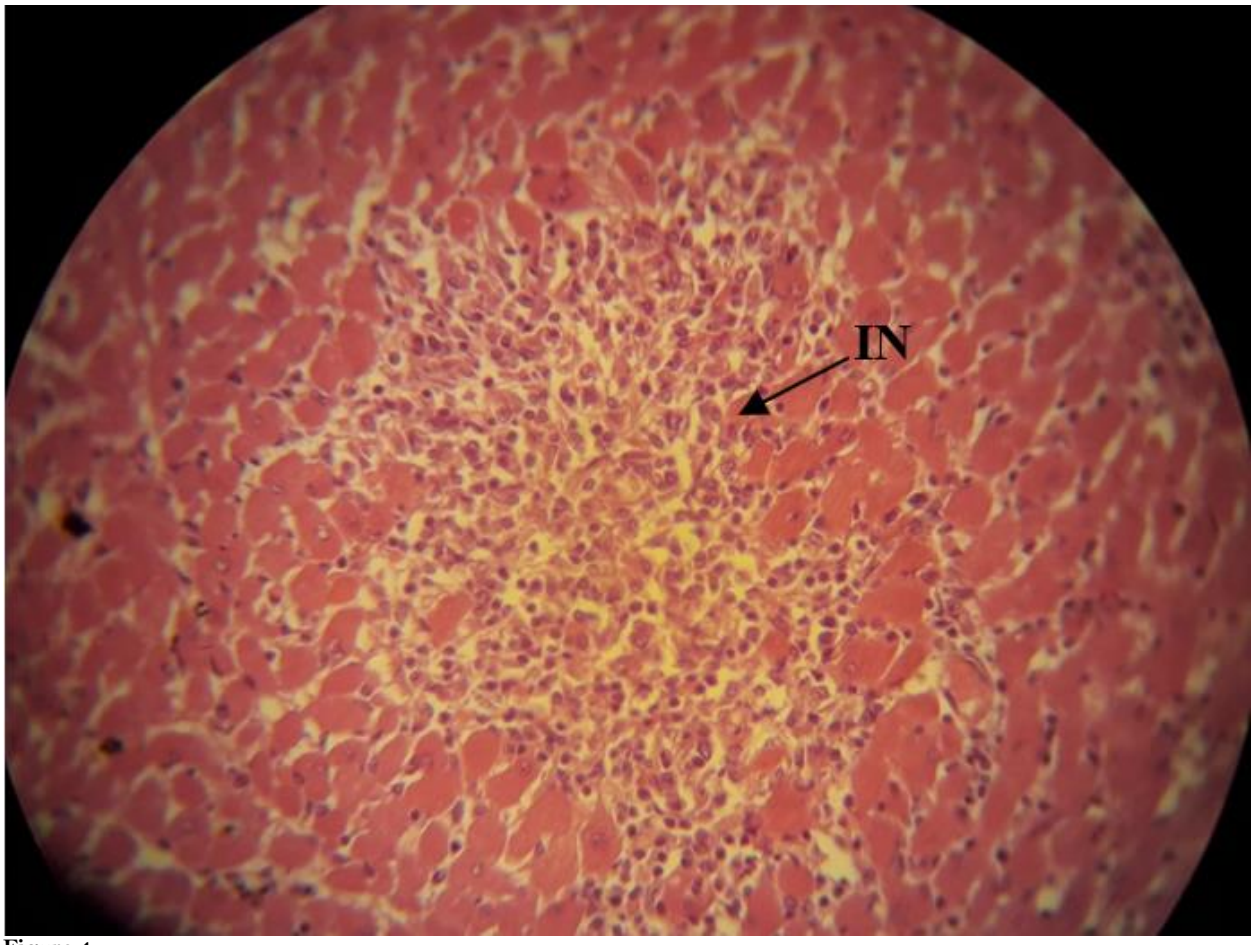

Figure 4.
Histological section of the heart of a pregnant female rat from 2nd group showing Infiltration (IN). H&E stain: 400X.

Remdesivir's possible adverse effects, particularly its impact on cardiac function, including bradycardia and arrhythmia, have drawn a lot of attention [20]. One possible mechanism of remdesivir's effect is direct cardiotoxicity caused by remdesivir's active form, which interacts with cellular components and disrupts intracellular metabolism.

The affinity of Remdesivir for viral RNA polymerase in comparison to human mitochondrial RNA polymerase (h-mtRNAP) determines its safety and efficacy. It has been discovered that Remdesivir has a 500-fold higher affinity for viral polymerases than for h-mtRNAP [21].

Even though viral RNA polymerase has a strong affinity for h-mtRNAP, it is still possible that h-mtRNAP will be involved and cause mitochondrial dysfunction, in fact drug-induced mitochondrial dysfunction from other sources is a known cause of the observed cardiotoxicity [22]. Some laboratory experiments have shown that remdesivir can cause damage to the mitochondria of cardiac muscle cells ,Mitochondria make up 30% of the volume of adult cardiomyocytes (CMs) and are essential for metabolism and apoptosis in the myocardium, therefore damage to this organelle can significantly impair heart function[23].

Remdesivir does not accumulate in the body, but after several once-daily doses, its metabolite GS-441524 (nucleoside monophosphate) reaches a steady state around day 4 and accumulate at a pace of about two times [24]. Furthermore, compared to the toxic effects of chloroquine on the heart, remdesivir can have substantial cytotoxic effects in cardiac myocytes. Remdesivir's attachment to human mitochondrial RNA polymerase causes cardiotoxicity [25].

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Finally, Healthcare workers should take remdesivir carefully and be aware of its possible cardiac effects, there is still an urgent need to evaluate the safety profile of remdesivir and the adverse cardiovascular effects resulting from its use.

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