Cardiovascular Side Effects of Neuraminidase Inhibitors: A Review

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Abstract. Neuraminidase inhibitors are antiviral drugs prescribed especially for influenza types A and B. They inhibit the release of the viral neuraminidase protein, which facilitates viral release from the infected cell to the other host's cells. There has been an increasing use of these drugs during the COVID-19 pandemic. However, few studies have examined the potential serious side effects on physiological systems, such as the cardiovascular system. This review evaluated the literature on the cardiovascular side effects of neuraminidase inhibitors. Articles from several catalogue databases such as PubMed, Science Direct, and journals published by Nature Publishing Group and BMJ, published in English from January 1, 2011, to July 30, 2021, were included. We found reports of cardiovascular adverse events related to the use of remdesivir, oseltamivir, peramivir, zanamivir, and laninamivir. Case reports of hospitalized COVID-19 patients indicated that the sinus bradycardia and prolonged QTc interval observed in patients were associated with remdesivir use and could be resolved with discontinuation of this neuraminidase inhibitor. Supraventricular tachycardia related to the use of oseltamivir in newborns was also reported. A preclinical study found that a high dose of oseltamivir may have increased cardiac preload and decreased contractility, which led to a decrease in cardiac output. Although rare, serious adverse events such as cardiac arrest or cardiac failure were reported after use of peramivir in the elderly. Other papers reported on the potential for cardiac arrest associated with remdesivir use. Similar cases were documented regarding the cardiovascular side effects of laninamivir that manifested as rare palpitations. The cardiovascular side effects associated with the use of neuraminidase inhibitors may vary depending on the dosage, patient's age and comorbidity. Despite the efficacy and safety profile of neuraminidase inhibitors, this review highlights a concern about the potential cardiovascular side effects related to the use of these drugs. Prescription of these drugs should be carefully monitored and assessed to anticipate serious adverse events.

Keywords: Neuraminidase Inhibitor · Oseltamivir · Remdesivir · Cardiovascular Adverse Effect

H. Nurdiyanto et al. (Eds.): ICCvD 2021, AHSR 52, pp. 10–17, 2023.
https://doi.org/10.2991/978-94-6463-048-0_3

1 Introduction

Neuraminidase inhibitors (NIs) are a group of drugs that alter the release of neuraminidase protein, a surface protein found in viruses. The main mechanism of action of this class of drugs involves splicing the sialic acid terminal receptor residue, which prevents the viral hemagglutinin from recognizing the receptor. Another proposed mechanism is by interacting competitively with the active site of neuraminidase, which decreases the rate of viral aggregation and spread [1]. Drugs classified as NIs include oseltamivir, zanamivir, peramivir, and laninamivir. These drugs are commonly prescribed in the treatment of influenza types A and B, and they are readily available in the market.

Influenza is a virus from the Orthomyxoviridae family. Each year, influenza infects around 120 million people worldwide [2], and this high infection rate has an estimated 12-billion US dollar loss in socioeconomic terms. One of available treatment for this disease was adamantane before reports of central nervous system damage caused by this drug [3]]. Vaccination is a promising preventative, but the high antigenic drift of the virus requires renewal of the vaccine formulas annually. The development of new antiviral agents is required [3, 4].

Two NIs, zanamivir and oseltamivir, were developed in 2001 [2], and peramivir was approved in 2011.The latter is seen as a solution for patients who cannot receive oseltamivir via the oral route or zanamivir through inhalation [5].

NI availability and use have been reported to have increased during the ongoing pandemic of coronavirus disease-19 (COVID-19), which causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6]. Along with other treatments, antiviral drugs that mainly block virus replication, such as NIs, protease inhibitors, and fusion inhibitors, are considered as alternative strategies in the treatment of COVID-19 [7].

A Cochrane systematic review concluded that influenza infection might increase cardiovascular mortality, especially among people with a history of cardiovascular disease [8]. Antiviral therapy for patients with influenza and its effects in preventing recurrent cardiovascular events and reducing mortality have been reported [9, 10], as have the adverse events related to NI use [11]. The most frequent adverse events of NIs are neuropsychiatric and gastrointestinal disorders. Cardiovascular side effects are rarely found, although some, such as cardiac arrest and cardiac failure, are categorized as serious adverse events [11]. Given the demand for NIs and concerns about the safety of NIs use, this review summarizes the recent literature on the types of cardiovascular side effects occurred after the use of NIs, types of NIs, and factors influencing the occurrence of adverse events.

2 Method

This review examined recently published journals (2010–2021) to identify articles on the cardiovascular effects after the use of NIs. The keywords used were “neuraminidase inhibitor”, “safety”, “adverse drug reaction”, “adverse event”, “cardiovascular”, and “influenza”. The databases searched for this review included PubMed, Science Direct, and journals published by Nature Publishing Group and BMJ. Google Scholar was also used to check the citations of publications.

3 Result and Discussion

This review summarizes the literature on the cardiovascular effects according to the type of NI: oseltamivir, remdesivir, peramivir, and laninamivir.

3.1 Oseltamivir

A meta-analysis concluded that the use of oseltamivir may reduce the incidence of cardiac events in adults. Compared with placebo, the corrected QT prolongation increased after oseltamivir administration [12]. However, in a case report, Bodo et al. (2020) described an event involving suspected supraventricular tachycardia (SVT) induced by oseltamivir [13]. A 4-month-old boy diagnosed with influenza A exhibited the SVT 30–40 min after the second dose of oseltamivir oral suspension (3 mg/kg/dose); the patient had his first dose at home. His heart rate was > 300 bpm and an electrocardiogram suggested SVT. There were no further episodes of SVT after discontinuation of oseltamivir [13]. This finding revealed a cardiac event that was not listed in the manufacturer's drug information for oseltamivir.

Bradycardia is another possible cardiac event after administration of oseltamivir. A recent retrospective study of 203 adults with influenza who received two doses of oseltamivir confirmed the occurrence of oseltamivir-associated bradycardia. In that study, 43% of critically ill patients developed bradycardia (heart rate $\leq$ 59 bpm) [14] The average onset of bradycardia was 51 $\pm$ 43 h after the first dose of oseltamivir. The treatment dosage regimens were 75 mg twice daily for patients with creatinine clearance > 60 mL/min, and a lower dosage for those with a lower creatinine clearance [14]. An association between bradycardia and oseltamivir use has been reported in case reports in both pediatric [15, 16] and adult patients [17, 18].

3.2 Remdesivir

A randomized, placebo-controlled trial of 237 patients with laboratory-confirmed COVID-19 reported adverse events in 102 of the 155 (66%) patients in the intravenous remdesivir group and 50 of 78 patients (64%) in the placebo group. The percentages of patients who discontinued their treatment because adverse events were 12% and 5% in the remdesivir and placebo groups, respectively. Respiratory failure and gastrointestinal disorders (e.g., nausea, vomiting) were the most common reasons for stopping the medication [19]. Among the adverse events observed, hypokalemia was reported in both the remdesivir and placebo groups. Serious adverse events related to the cardiovascular system, including cardiopulmonary failure and cardiac arrest, were rarely found. There were no deaths during the period of treatment associated with remdesivir administration [19].

A case report involving two COVID-19 patients observed sinus bradycardia within 20–40 min after intravenous administration of remdesivir. After the third dose, the heart rate dropped from 80–100 bpm to 40–50 bpm and returned to normal once remdesivir was discontinued [20]. Similarly, two recent case reports reported bradycardia-related adverse events associated with remdesivir in COVID-19 patients. These events included

a sudden decrease in heart rate after administration of remdesivir and gradual return to normal once the medication was stopped [21, 22].

A case–control study involving 46 COVID-19 patients found that bradycardia was more likely to occur in the remdesivir group (60%) than in the control group (23%) [23]. There were no alterations in blood pressure and ECG patterns. However, this study highlighted the need for awareness of the potential of remdesivir-related bradycardia, especially for patients who take medications that might induce bradycardia (e.g., beta-blockers).

A pharmacovigilance study of cardiac arrhythmias in COVID-19 patients compared cases of bradycardia after remdesivir with those after other medications (hydroxychloroquine, lopinavir/ritonavir, tocilizumab, or glucocorticoids). This study reported that 302 of 2603 patients who received remdesivir developed cardiac adverse events and that 94 (31%) of them involved bradycardia. Sixteen of 94 cases could have progressed to life-threatening bradycardia without treatment. The authors of this study concluded that remdesivir has a higher risk of inducing bradycardia than other medications studied [24]. However, a randomized controlled trial of safety outcomes after remdesivir treatment in 1062 COVID-19 patients found that 24.6% of patients in the remdesivir group reported serious adverse events. This percentage was lower than that found in the placebo group (31.6%) [25].

ECG alterations are another cardiac safety signal related to remdesivir use. A case report noted a prolongation in the QTc interval and T wave abnormality in a 26-year-old COVID-19 patient after the third dose of remdesivir. The QTc interval increased from 439 ms to 555 ms but stabilized after remdesivir was discontinued [20]. The risk of drug-induced long QT syndrome with remdesivir use was assessed based on literature review and computing database information. Intravenous administration of remdesivir was shown to induce a high drug concentration within the plasma volume, which may lead to prolongation of the QT interval and torsade de pointes [26].

Prolongation of the QRS complex is another ECG alteration associated with remdesivir therapy. A case report described a 54-year-old COVID-19 patient with a history of left bundle branch block, hypertension, and beta-cell lymphoma. The patient's use of rituximab had stopped several weeks before admission, and use of lenalidomide stopped on the day of admission. QRS complex prolongation, along with sinus bradycardia and alarming signs, such as dizziness, persistent chest pain, and shortness of breath, occurred 2 days after remdesivir administration (200 mg loading dose and 100 mg/day). After remdesivir was stopped and atropine was given, the QRS normalized, pain subsided, and heart rate stabilized [21].

Currently, there is no specific pathophysiology that can explain the reasons for ECG changes related to remdesivir. The active metabolite form of remdesivir, triphosphate nucleotide, has a similar structure to adenosine triphosphate (ATP) and may cause slowing of the sinoatrial node in terms of automaticity of heart electroactivity. This similarity to ATP may also alter the heart physiology by interacting with the sensory vagus nerve. Another possibility is that abnormal levels of proinflammatory cytokines in COVID patients may alter the sinoatrial node by slowing its electrical activity. Findings related to ECG changes after remdesivir administration indicate the need to monitor the ECG during therapy, especially for patients with underlying cardiovascular disease [27].

3.3 Peramivir

Peramivir was approved by the US Food and Drug Administration (FDA) in 2014 as a medication for adult patients without complications and is considered effective for pediatric patients with influenza [28]. A case report noted the effectiveness of a single dose of 300 mg of peramivir (intravenous) in a 45-year-old Korean woman diagnosed with severe influenza A complicated by fulminant myocarditis [29]. Given its effectiveness and formulation, intravenous peramivir is a choice when other antivirals are ineffective or in patients who cannot tolerate other medications [5, 30].

A real-world data safety profile was reported for 1199 pediatric patients treated with peramivir. The incidence of adverse drug reactions (ADRs) was 7.7% and included mainly diarrhea and abnormal behavior. The presence of underlying disease was a significant factor related to ADR incidence [28]. A review summarized the data for the safety and tolerability of peramivir and found hypertension to be a commonly reported ADR after peramivir use [30]. Another review of several studies concluded that gastrointestinal disorders such as diarrhea, nausea, and vomiting are the most common adverse events of peramivir [5]. Some studies have identified rare adverse events related to peramivir such as myasthenia gravis and immune thrombocytopenia [30]–[32]. In 2020, data from the FDA Adverse Event Reporting System (FAERS) found that most adverse events associated with peramivir based on FAERS data were cardiac and vascular disorders. Among the elderly (aged $\geq$ 65 years) adverse events related to peramivir included abnormal hepatic function, cardiac failure, shock, and cardiorespiratory arrest [11].

3.4 Zanamivir

FAERS data show that zanamivir is generally safe and that adverse events related to zanamivir include general disorders and bruising at the administration (injection) site [11]. Marty et al.[33] reported findings of a randomized, double-blind, phase 3 clinical trial involving 626 hospitalized influenza patients in 26 countries. The incidence of adverse events was similar in the three treatment groups: intravenous zanamivir 300 mg, intravenous zanamivir 600 mg, and oral oseltamivir 75 mg. Diarrhea, respiratory failure, and constipation were the most frequent adverse events.

Cardiovascular events associated with zanamivir are rarely reported. A randomized, placebo-controlled study involving 46 healthy adults found that administrations of zanamivir did not alter cardiac repolarization [34]. Among the patients hospitalized with severe influenza, cardiac arrest and cardiac failure were reported as rare serious adverse events (0.49%), but the rates of these events were similar in the groups treated with intravenous zanamivir and oral oseltamivir [33]. A review indicated that intravenous zanamivir has favorable effects in critically ill influenza patients when oral NIs are not feasible or when resistance to other NIs (e.g., oseltamivir) has occurred [35].

3.5 Laninamivir

Postmarketing surveillance to assess the safety of a single inhalation of laninamivir reported ADRs in 50 of 3542 (1.41%) patients. The most common ADRs were psychiatric and gastrointestinal disorders. Cardiac disorders such as palpitations were rarely

observed and were recorded for only one of 3542 patients (0.03%) [36]. Another recent postmarketing study reported a 1% incidence of ADRs related to laninamivir use in children under the age of 5 years and observed no serious cardiovascular ADRs [37].

4 Conclusion

This review discussed the types of adverse events related to NIs especially in the cardiovascular system. Generally, cardiac side effects of NIs are rare. The severity of the side effects observed are related to the dosage or factors in the patient's background such as age and comorbidity. The increasing demand and availability of NIs during the pandemic require close monitoring of possible side effects and adverse events.

Acknowledgment. Authors thank the Faculty of Medicine Universitas Islam Indonesia for supporting the presentation of this paper.

Author's Contribution. Analysis of search findings and drafting the manuscript were performed by SZ, FM, MA, and RM. RR contributed to the conceptualization, critical review, and manuscript writing. All authors discussed the findings.

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