Review Article

The Concomitant Use of Melatonin and Molnupiravir in the Treatment of COVID-19: Mini Review

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Abstract

With the ongoing pandemic declared by the World Health Organization,the number of hospitalizations and deaths caused by COVID-19 is increasing dramatically. As new variants of SARS-CoV-2 emerge, new combination therapies are needed to reduce the risk of COVID-19spreadduring this time of increased transmission risk. In this case, it is vitalto strengthen the immune system against highly inflammatory conditions such as the cytokine storm caused by COVID-19. This brief review highlights the benefits of taking melatonin and the new antiviral drug molnupiravir together in the treatment of COVID-19. Webelieve that this combination therapy against COVID-19 would be of great benefit and should be considered as an adjuvant therapy in the treatment of this disease.

Keywords: Molnupiravir; melatonin; cytokine; SARS-CoV-2; COVID-19

Bangladesh Journal of Medical Science Vol. 22 No. 01 January'23 Page : 32-37
DOI: https://doi.org/10.3329/bjms.v22i1.61857

Introduction

The World Health Organization (WHO) declaredcoronavirus disease (COVID-19) a pandemic in early March 2020[1]. Since then, thousands of people have become ill and died from COVID-19. Since the start of the pandemic, several COVID-19 studies have been conducted to addressthe different approaches and strategiesto manage the COVID-19 disease[3]. In a previous study, ARIMA, Brown's single exponential smoothing model,and double exponential smoothing models were used to model the pandemic and predict indicators with different time series models[3]. The obtained datawere collected from 25 different countries and the estimated values were obtained separately from each country[3].

TheOmicron variantresponsible forincreased infectivity and decreased efficacy of existing treatments was designated as avariant ofconcern by the World Health Organization in November 2021[4]. Omicron, also known as B.529,is a novel variant of SARS-CoV-2 with a high number of mutations compared with other variants, leading to a substantial increase in the number of cases afterinitial confirmation[5,6]. Therefore, new strategies

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for the treatment ofSARS-CoV-2 disease are urgently needed, not only to reduce the potency of the virus, but also to eliminate severe virus-related inflammatory conditions such as cytokine storm.

SARS-COV-2,a viruswrappedinasingleRNA,attacks the cell via the viral structural spike protein(S),that binds to angiotensin converting enzyme-2(ACE2) receptors[7].The host transmembrane serine protease type 2 (TMPRSS2) facilitates entry into the cell via the S protein[8]. Once inside the cell,viral polyproteins encodingthereplicase-transcriptase complex are synthesized. When SARS-CoV-2 binds to ACE2 receptors and the serine protease TMPRSS2 to activate the prime Sprotein in airway epithelial cells, it triggers an inflammatory response and leading to cytokine storms and acute respiratory distress syndrome[9,10].

Cytokine storm syndrome is caused by a variety of inflammatory conditions, including severe systemic inflammation, hemodynamic instability, and multi-organ failure.In addition, oxidative reactions cause reactive oxygen species (ROS)-mediated damage in the lungs, particularly in the alveoli[12]. As COVID-19 has reached an unpredictable number of infections and deaths, the FDA has approved some drugs for emergency use due to this situation[13]. One of the most promising of these drugs is molnupiravir, a new antiviral agent in the form of a prodrug that is activated by intracellular phosphorylation to its triphosphate form which is incorporated into viral RNA, causes the accumulation of deleterious errors that prevent viral replication[14,15]. In addition to the abovetreatments, there is another basic method to increase resistance to the virus, which is related to the biological rhythm. The menstrual cycle is the most basic and important circadian rhythm[16]. Melatonin, a hormone secreted by the brain primarily at night, helps maintain the body's biological clock and regulate its rhythm[17]. With a synchronized circadian rhythm in the lungs, heart, kidneys and brain, the immune system can effectively fight off viral infections[18,19].

Molnupiravir in SARS-CoV-2 treatment and its effect on new Omicron variant

Molnupiravir is a new oralantiviral drugrecently approved for COVID-19[20]. It exerts its antiviral effect by causing transcription errors by replacing cytidine in newly formed RNA during viral RNA replication[21]. In addition, molnupiravir differs from other similarly acting antiviral agents in that it can bypass the exonuclease repair action of SARS-CoV-2[22]. Molnupiravir has alreadydemonstrated*invitro* activity against SARS-CoV-2 in cultures of human respiratory epithelial cells. SARS-CoV-2 treated with molnupiravir showed improved lung function and decreased viral titers[23]. Molnupiravir has also been reported to suppress SARS-CoV-2 replication in human lungmodels (LoM)[24] and from Syrian hamsters when administered 12 hours before or after infection[25]. In COVID-19 clinical trials,molnupiravir and dexamethasone have been shown to produce good resultshospitalized patients[26]. Treatment with molnupiravir has been reported to reduce the risk of death by 50% in newly diagnosed high-risk COVID-19 patients[26]. Plemer et al. demonstrated that molnupiravir was effective against SARS-CoV-2 when administered orally and suppressed viral transmission to untreated contacts within 24 hours[27]. The phase 3MOVeOUT trial reported thattreatment with molnupiravir significantly reduced hospitalizations when initiated within 5 days of the onset of signs and symptoms of COVID-19[28]. This study was conducted in unvaccinated adults who were at risk forprogression to severe disease and resultsof the study showed that molnupiravir was effective agent with no safety concerns.

Over the past year, several variants have emerged as a result of multiple mutations of the SARS-CoV-2 virus spike protein[29].The Omicron variant, which is currently spreading worldwide, is believed to contain more mutations and is much more contagious than earlier variants[30]. In addition to the rapid spread of the new variant, studies ofmolnupiravir have also gained momentum. A recent study evaluated the efficacy of molnupiravir on the Omicron variant using an isolate from an infected patient in the Netherlands[31]. Compared with earlier variants, Omicron has been shown to have a lower diffusion capacity in Calu-331 human lung epithelial cells. Treatmentwithmolnupiravir showed potentdose-dependent inhibition of viral replication in these cells. This study demonstrates that molnupiravirremains an effective and preferred antiviral agent for SARS-CoV-2 Omicron variant infection.

The fact that the mechanism of action of molnupiravir is independent of mutations in the SARS-CoV-2 spike protein and maintains its efficacy against multiple variants is more advantageous than other therapeutic options such as certain monoclonal antibodies, whose efficacyis weakeneddue to a high number of mutations in the receptor-binding domain of the virus, as reported in recent studies[32- 34]. In

addition, oral antiviral agents such as molnupiravir have the advantage of being easier to manage and more availability than other therapeutic agents administered by injection for the treatment of COVID-19.

Effects of melatonin on the immune system and viral infections

Zhuang et al demonstrated the relationship and role of circadian rhythms in altering the susceptibility of lung epithelial cells to SARS-CoV-2 infection[35]. According to this study, deletion of the essential circadian transcriptional activator Brain and Muscle ARNTlike protein1 (BMAL1) led to a decrease in the expression of the primary viral receptor ACE2 andentry of the virus into lung epithelial cells. Decreased levels of the BMAL1 gene, which regulates circadian rhythms, trigger a cascade of events leading to cytokine storms via the NFκB pathway, as seen in COVID-19[36]. In addition to the interaction between protein S and ACE2,SARS-CoV-2 has been shown tointeract directly with Cluster of Differentiation 147 (CD147)[37, 38], a type I transmembrane protein involved in viral infection[39].

Melatonin is an effective treatment option for the prevention of severeCOVID-19 symptoms due to its known anti-inflammatory, immunomodulatory and antioxidant properties[40]. Melatonin is not virucidal but has indirect antiviral effects[41]. In addition, melatonin has been shown to reduce acute lung injury, stroke,virus-mediated death, and viral activity by regulating serum levels of IL-2 and IFN-γ, which are key factors in the inflammatory pathway mediated by CD147[42,43].

Melatonin is a potent stimulant of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase and provides significant protection against oxidative damage to cells[44]. Melatonin receptors (MT2) have also been identified on spleen cells[45]. External application of melatonin has been reported to increase the proliferationof spleen cells in rodents such as miceand hamsters, and MT2 receptors play an important role in this stimulatory effect of melatonin[46,47]. In addition,treatment with melatonin increases the proliferation of Tcells[48]. In this case, the ability of macrophages to present antigens to T lymphocytes is facilitated. In immunocompromised mice, melatonin increased the activity of weakened helper T cells, while an increase in endogenous opioids released by helper T cells was observed when T cells were stimulated by melatonin[49]. These endogenous opioids have a stimulatory effect on immune function. In mice, endogenous opioids derived fromT helper cells increase antibody synthesis[50]. When melatonin is administered to aged mice, thymic function and lymphocyte-mediated immune functions T cell-mediated immune functions reach the same level as young mice[51]. Melatonin decreases T cell apoptosis and increases the expression of T cell-mediated cytokines[52]. Melatonin administrationincreases the release of IL-2, IL-6, IFN-γ, IL-1 and IL-12 from human monocytes[53]. Thesecytokines may prevent stress-induced immunosuppression or secondary immunodeficiencies. In addition, uncontrolled inflammatory mediators releasedin COVID-19 cause acute respiratory distress syndrome (ARDS) and cytokine storm syndrome[54]. It has been reportedthat theimmunosuppressive effects of corticosteroids such as dexamethasoneregulate the deleterious effects of cytokines by decreasing cytokine levels[55,56]. Like dexamethasone, melatonin also reduces this cytokine storm by increasing natural killer cell activity and decreasing reactive oxygen species, interferon-gamma response, and T-helper cells[57] (Figure 1).Melatonin also reduces the hyperinflammatory response to these respiratory viruses by inhibiting NFκB activity like dexamethasone[58]. At higher doses, melatonin increases the production of interleukins. These interleukins increase the inflammatory response caused by the lunginfection resulting from these viral infections[59]. In mice infected with respiratory syncytial virus (RSV), treatment with melatonin suppressed the production of malondialdehyde and nitric oxide, which explains the reason for the reduction in acute oxidative damage in the lungs[60].

Conclusion

In conclusion, understanding how viruses interact with the circadian rhythms of infected patients may influence the clinical management and treatment of viral infections. Therefore, circadian modulatorsuch as melatonin may be useful for the treatment of viral infections and the efficacy of molnupiravircould be optimized when it is co-administered with melatonin. We believe that this combination therapy would improve COVID-19 treatment outcomes and reduce potential side effects, especially in high-risk patients and the elderly.

Author contribution statement

All authors have equally contributed to the study.

Ethical Approval

None applicable.

Funding

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

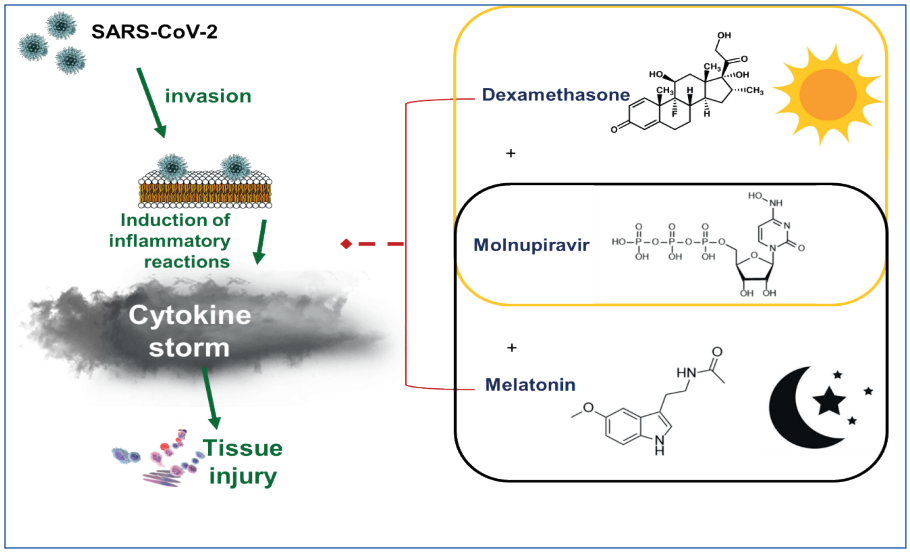

Figure 1. Schematic demonstration of the mechanistic pathway for melatonin and molnupiravir

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