Review Article

2-Deoxy-D-Glucose: A Ray of Hope in COVID Pandemic

Priyotosh Banerjee, Indrani Devi Sarma, Dasgupta Himadri Sekhar, Dhriti Kumar Brahma, Melambha Surong
Department of Pharmacology, NEIGRIHMS, Shillong, Meghalaya, India

Abstract

Coronavirus disease-19 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 is a respiratory tract infection that has already made a huge negative impact in global health situation. Transmission mainly occurs through droplets, and the virus is highly contagious. Mainly symptomatic treatments are given at present with some drugs for serious patients with unproven efficacy and safety. In this context, Institute of Nuclear Medicine and Allied Sciences, a research laboratory of Defence Research and Development Organization in collaboration with Dr. Reddy's Laboratories, Hyderabad, has introduced a new medicine named 2-Deoxy-d-glucose (2-DG) (which has been previously tried in cancer) for the treatment of seriously ill COVID patients with a target to reduce the oxygen demand. Clinical trials showed evidence that 2-DG effectively reduces oxygen requirement in seriously ill patients, and real-time polymerase chain reaction conversion is also faster. Recently, 2-DG is approved for the use in critically ill patients by the Drug Controller General of India in May 2021. The introduction of 2-DG brings a new hope in reducing the mortality in COVID patients.

Keywords: 2-Deoxy-D-Glucose, Defence Research and Development Organisation, Drug Controller General of India, severe acute respiratory syndrome coronavirus 2

Introduction

The whole world has been affected by the coronavirus disease-19 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), a dreaded virus in coronaviridae virus family.[1] Initially reported as an epidemic beginning in Wuhan province, China, on February 2020, turned into a pandemic as declared by the World Health Organization (WHO) in March 11, 2020.[2] Like other coronavirus, it is also a respiratory tract virus, for example, SARS, MERS, etc. Initial discovery was also made in human tracheal cell culture, way back in 1965.[3] The transmission mainly occurs through the droplets from human to human, and recently few data are showing it to spread through aerosol formation as well.[4] As the virus is very highly contagious and because of present day's ease in travel, the infection spreads very quickly over the whole world. Moreover, most of the infected people are either asymptomatic or symptoms are very mild to notice, but they are capable of spreading the disease in other people.[5] The symptoms are similar to common cold or viral pneumonia, such as fever, cough, sore throat, headache, and fatigue[6] and are the reasons why the infection is tough to detect clinically. Only rapid antigen test or real-time polymerase chain reaction (RT-PCR) can identify new infections as well as assessment of antibody for any previous infection.[7] Regarding the treatment of COVID-19 currently, there are no specific antiviral drugs and various treatment options are attempted globally. As an added treatment of COVID-19 2-Deoxy-d-glucose (2-DG) has recently been approved by the Drug Controller General of India (DCGI) recently. This mini review is being attempted to provide some clinicopharmacological information regarding this newly introduced drug.

Problem Statement and Pathogenesis of COVID-19

As per the WHO update on global coronavirus cases on August 3, 2021, over 4 million new cases have been detected with 64,000 new deaths globally during the previous 1 week.

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.jpp_69_21

Address for correspondence: Dhriti Kumar Bramhma, Department of Pharmacology, NEIGRIHMS, Shillong - 793 018, Meghalaya, India.
E-mail: dbdhriti168@gmail.com

How to cite this article: Banerjee P, Sarma ID, Sekhar DH, Brahma DK, Surong M. 2-deoxy-d-glucose: A ray of hope in covid pandemic. J Pharmacol Pharmacother 2021;12:107-9.

Received: 10-06-2021 **Revised:** 10-08-2021
Accepted: 16-08-2021 **Web Publication:** 25-11-2021

However, death rate has been declined, while increase in new cases pose a challenge. The world already faced the devastating impact of COVID pandemic in the 1st wave and in the current 2nd wave, the problem continues. The problem is more serious in South-east Asia where daily new patients are increasing rapidly with weekly around 22,000 deaths.[8] Death mainly occurs due to the development of hypoxia, acute respiratory distress, and widespread tissue damage leading to multiorgan failure due to cytokine storm.[9] This virus mainly affects the respiratory system by entering through ACE 2 receptor, resulting in acute lung injury and pulmonary edema.[10] The clinical features range from asymptomatic to milder cases showing fever, sore throat, anosmia, mild gastrointestinal symptoms whereas serious cases present with respiratory insufficiency as decreased oxygen saturation.[11] Hence, therein lies the importance to find a proper treatment protocol for COVID-19 infection.

Treatments Available

Since the beginning of COVID-19 pandemic, scientists in various countries are conducting research to modulate the treatment protocol for the pandemic. Initially, treatment modalities were limited to symptomatic treatment and break the contamination chain. Later on various studies reveal drugs which are capable to mitigate the severity. Drugs such as doxycycline and Ivermectin showed promising results in clinical trials.[12] Later on, specific antiviral drugs such as Remdesivir, lopinavir/ritonavir, and furthermore, casirivimab and imdevimab; an antibody cocktail, bamlenivimab and etesevimab combination, corticosteroids, tocilizumab came out into effect and were recommended by different drug regulatory authorities.[13] Now most recently DCGI recommended 2-DG as a new drug for the treatment against COVID-19.[14]

2-Deoxy-D-Glucose FACTS

2-DG is a glucose molecule which has the 2–OH group replaced by hydrogen, which prevents it from glycolysis. Acting as an analog of mannose causes competitive inhibition of 2– deoxyglucose– 6– PO_4 on glucose– 6– PO_4 at phosphoisomerase level, resulting in primary block in glucose catabolism.[15] Hence, those cells with higher rate of glucose usage gets affected more by 2-DG-induced metabolic inhibition. That's why 2-DG has been extensively tried in cancer therapy trials alone and also with fenofibrate (a hypolipidemic drug).[16] It has been also tried in temporal lobe epilepsy where it was seen to reduce kindling of neuronal cells.[17] 2-DG also binds irreversibly to viral endoribonuclease and main protease 3CL-pro in a spontaneous manner, and the binding is stronger compared to other antiviral drugs, such as lopinavir. This results in inhibition of viral capsid formation and improper replication.[18] In various dose escalation studies, it has been observed that the drug is well tolerated at a dose of 63 mg/kg/day; however, QT prolongation which is an adverse event, is seen in around 66% of patients.[19] Now 2-DG is approved for COVID by DCGI.[14]

2-Deoxy-D-Glucose IN COVID

Metabolic alterations in COVID infection have been demonstrated in various studies. Studies suggest that there is increase glycolytic activity and glucose reserve in immune cells, like monocytes infected with SARS CoV-2, contrary to the infection with influenza A or respiratory syncytial virus (RSV).[20] Hence, glycolysis acts as a good source of carbon as well as ATP, required to maintain the metabolic reaction in these cells.[21] Moreover, glucose plays an important role in SARS CoV–2 replication of human infected cells as shown in various studies. The two most common mechanisms of glucose metabolism include glycolysis and glycosylation.[22] It has also been reported that the expression of inflammatory genes is glucose dependent and this is blocked by 2-DG-mediated inhibition of glucose metabolism.[20] On the basis of this phenomenon, Institute of Nuclear Medicine and Allied Sciences, a research laboratory of Defence Research and Development Organization (DRDO) in collaboration with Dr. Reddy's Laboratories (DRLs), Hyderabad, conducted a clinical trial on 2-DG to establish its activity against COVID-19 infection. Phase II trial was approved in May, 2020 (CTRI/2020/06/025664) which was conducted during May-Oct, 2020 on 110 COVID patients. Phase III trial was conducted at 27 COVID hospital across multiple cities in India from December 2020 to March 2021 in 220 patients, which showed significantly higher proportion of patients improving symptomatically and oxygen support has been weaned off, in 42% in 2 DG group compared to 31% in standard of care arm. Similar trends were seen in patients aged 65 years and above. Furthermore, there is higher RT-PCR conversion rate in 2-DG arm. Finally, DCGI has approved 2-DG as COVID therapy in May 8, 2021. It has been approved for emergency use in COVID patients requiring higher O_2 support.[14]

Summary

COVID-19 has become pandemic since late 2019 worldwide and 167 million people globally and 26 million people infected in India. DRDO has initiated clinical trial with a previously known drug 2-DG in COVID patients which shows promising result in phase III clinical trial. The drug got its approval for COVID treatment by DCGI in May 8, 2021.[14] There is a possibility of its availability in early June as declared by DRL[23] and to be marketed in sachet. However, more safety data are required to establish its safety.[24] However, 2-DG has indeed brought a light of hope in reducing mortality in seriously ill COVID patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Lebow JL. Family in the age of COVID-19. Fam Process 2020;59:309-12.
2. Dos Santos WG. Natural history of COVID-19 and current knowledge on

treatment therapeutic options. Biomed Pharmacother 2020;129:110493.
3. Kahn JS, McIntosh K. History and recent advances in coronavirus discovery. Pediatr Infect Dis J 2005;24:S223-7226.
4. Zhang R, Li Y, Zhang AL, Wang Y, Molina MJ. Identifying airborne transmission as the dominant route for the spread of COVID-19. Proc Natl Acad Sci U S A 2020;117:14857-63.
5. Duarte NA. Can people with asymptomatic or pre-symptomatic COVID-19 infect others: A systematic review of primary data. MedRxiv 2020; Available from: https://doi.org/10.1101/2020.04.08.20054023.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
7. Goudouris ES. Laboratory diagnosis of COVID-19. J Pediatr (Rio J) 2021;97:7-12.
8. WHO weekly update on COVID-19; 51;2021. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---3-august-2021.
9. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J 2020;55:2000607.
10. Pandey P, Agarwal S, Rajkumar. Lung pathology in COVID-19: A systematic review. Int J Appl Basic Med Res 2020;10:226-33.
11. Azer SA. COVID-19: Pathophysiology, diagnosis, complications and investigational therapeutics. New Microbes New Infect 2020;37:100738.
12. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, *et al*. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis 2021;103:214-6.
13. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.2021 Jul 30. Available from: https://pubmed.ncbi.nlm.nih.gov/32150360/.
14. Ministry of Defence; DCGI Approves Anti-COVID Drug Developed by DRDO for Emergency Use". Press Information Bureau, Government of India; May 08, 2021. Available from: https://pib.gov.in/PressReleasePage.aspx?PRID=1717007.
15. Wick AN, Drury DR, Nakada HI, Wolfe JB. Localization of the primary metabolic block produced by 2-deoxyglucose. J Biol Chem 1957;224:963-9.
16. Liu H, Kurtoglu M, León-Annicchiarico CL, Munoz-Pinedo C, Barredo J, Leclerc G, *et al.* Combining 2-deoxy-D-glucose with fenofibrate leads to tumor cell death mediated by simultaneous induction of energy and ER stress. Oncotarget 2016;7:36461-73.
17. Garriga-Canut M, Schoenike B, Qazi R, Bergendahl K, Daley TJ, Pfender RM, *et al.* 2-Deoxy-D-glucose reduces epilepsy progression by NRSF-CtBP-dependent metabolic regulation of chromatin structure. Nat Neurosci 2006;9:1382-7.
18. Balkrishna A, Thakur P, Singh S, Dev SN, Jain V, Varshney A. Glucose antimetabolite 2-Deoxy-D-Glucose and its derivative as promising candidates for tackling COVID-19: Insights derived from in silico docking and molecular simulations. Authorea. July 08, 2021; DOI: 10.22541/au.158567174.40895611/v2.
19. Raez LE, Papadopoulos K, Ricart AD, Chiorean EG, Dipaola RS, Stein MN, *et al*. A phase I dose-escalation trial of 2-deoxy-D-glucose alone or combined with docetaxel in patients with advanced solid tumors. Cancer Chemother Pharmacol 2013;71:523-30.
20. Codo AC, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, *et al.* elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis-dependent axis. Cell Metab 2020;32:437-46.e5.
21. Bojkova D, Klann K, Koch B, Widera M, Krause D, Ciesek S, *et al.* Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature 2020;583:469-72.
22. Ghosh B, Roy S, Singh JK. The Mode of Therapeutic Action of 2-deoxy D-Glucose: Anti-Viral or Glycolysis Blocker? ChemRxiv. Cambridge: Cambridge Open Engage; 2021. Available from: https://chemrxiv.org/engage/chemrxiv/article-details/60e078d25cb3f6238591e424.
23. Koshy, Jacob (2021-05-11). "Questions remain on DRDO's COVID drug". The Hindu; ISSN0971-751. Available from: https://www.thehindu.com/news/national/questions-remain-on-drdos-covid-drug/article34537596.ece.
24. DRDO Releases anti-COVID drug; reduces oxygen dependency in patients, Business Standard; May 17, 2021. Available from: https://www.business-standard.com/article/current-affairs/rajnath-singh-releases-first-batch-of-anti-covid-drug-developed-by-drdo-121051700978_1.html.