Inhaled Nitric Oxide for postexposure chemoprophylaxis of COVID-19

Antoine AbdelMassih (antoine.abdelmassih@kasralainy.edu.eg)
Cairo university
Rafeef Hozaien
Meryam El Shershaby
Aya Kamel
Habiba-Allah Ismail
Mariem Arsanyous
Nadine El-Husseiny
Noha Khalil
Youstina Naeem
Raghda Fouda

Systematic Review

Keywords: Inhaled Nitric Oxide, COVID-19, Furin Inhibition, Postexposure prophylaxis

Posted Date: June 14th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-612293/v1

Abstract

Background:

Postexposure prophylaxis has been an overlooked strategy in the context of COVID-19. Inhaled Nitric Oxide offers itself as a potential tool in this context. The aim of this systematic review was to depict previous in vivo and in vitro studies demonstrating an antiviral role for NO

Methodology:

Embase, Medline and the Cochrane Central Register were used to search for specific keywords such as “Nitric oxide” AND “Antiviral activity” for relevant publications up to 1st of June 2021. The systematic review was performed using PRISMA protocol

Results:

Twenty-one studies were identified depicting an antiviral role for Nitric Oxide. Those studies involved sixteen viruses. Only four of the depicted studies were clinical trials, while three were performed on a murine model. The remainder of the studies involved in vitro experimentation of the role of NO in halting viral replication of several viruses including SARS-CoV-2

Conclusion:

While early reports of NO role in the treatment of COVID-19 suggested its use for the treatment of established ARDS, NO seems to have a much earlier and more efficient prophylactic role. It inhibits a protease needed for canonical viral replication of SARS-CoV-2, namely Furin, by decreasing calcium's cytosolic levels. This might add a significant tool for postexposure chemoprophylaxis in the at-risk group, especially medical personnel.

Introduction

SaNOtize (Canada (Vancouver-based/ NCT04443868 biotech firm) recently created a self-administered nitric oxide nasal spray (NONS) that is said to potentially reduce Coronavirus Disease 2019 (COVID-19) viral load in recently infected patients. After completing early-stage clinical trials in Canada and the United Kingdome (UK), SaNOtize, Ashford and St. Peter's Hospitals, the National Hospital System (NHS) foundation, and a few pathology services in the UK announced the results of Phase II trials. The results indicate that NONS can be a powerful and safe antiviral treatment. It could prevent COVID-19 transmission, shorten its duration and reduce the severity of its symptoms.

Several reports have discussed Nitric oxide use in the context of COVID-19. Lotz et al., for example, highlighted its potential to improve acute respiratory distress syndrome in COVID-19. However, the aforementioned clinical trial results suggest that it has a much earlier antiviral role in COVID-19. The exact mechanism of how it executes this role will be discussed in this report.(1)

Methodology

Embase, Medline and the Cochrane Central Register were used to search for specific keywords such as “Nitric oxide” AND “Antiviral activity” for relevant publications up to 1st of June 2021. The systematic review was performed using PRISMA protocol. Study Selection criteria Population: No specific age group or sex Intervention: Nitric oxide Comparison: No comparison has been a purpose of the study Outcome: Antiviral activity (in vivo or in vitro)

Results

Twenty-one studies were identified depicting an antiviral role for Nitric Oxide. Those studies involved sixteen viruses. Only four of the depicted studies were clinical trials, while three were performed on a murine model. The remainder of the studies involved in vitro experimentation of the role of NO in halting viral replication of several viruses including SARS-CoV-2.

Table 1 exposes the clinical and laboratory trials which used NO as an antiviral agent)(4–24)

Discussion

-Protease, a critical role in the determination of viral load of COVID-19

One of the very prominent members of the PCSK (pro-protein convertase subtilizing/Kexin) family is the Furin enzyme. Furin is a type 1 membrane-bound protease utilized by multiple pathogens, including Human Immune Deficiency Virus (HIV), Ebola virus, Marburg virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and even some bacterial toxins. It is believed that the pathogenicity of several viruses can increase several folds once they react with Furin and other Pro-protein convertases. This mechanism revolves around the activation of latent precursor proteins into their active products following Furin cleavage. Hence, Furin-dependent infections may respond to therapeutics targeting host cell Furin. (2)

As previously mentioned, the spike protein of SARS-CoV-2 is the cleavage site of Furin, which plays an essential role in the host range as well as viral infectivity and pathogenesis. As one of the subtilisin-like proteases, Furin requires a polybasic rather than a monobasic cleavage site; hence, cleavage occurs at the junction of the two polybasic subunits of the spike, S1 and S2. The difference in pathogenicity between highly virulent and less virulent influenza strains sets an excellent example of the relationship between viral pathogenicity and the biochemically different cleavage sites.(3)

-How viral protease activity is inhibited by intracellular cations and how NO increases such cations

Furin is a cellular enzymatic protein that is expressed from the FURIN gene in humans. It has been stated that Furin shows an intriguing interplay with intracellular ions, especially cations. Potassium ions are the most common intracellular ions in our bodies, and magnesium falls in the second rank, where it reveals

its direct correlation in activating Furin. Molloy et al. specified that calcium level, where Furin can be classified as a "Calcium-dependent enzyme, noticeably influence the activity of Furin. (25)

Moreover, Yamada and colleagues have added further demonstrations supporting the interrelation between Furin and calcium levels. The latter postulation is proved by the effect of Furin hindrance in restricting the escalation of neuronal damage caused by calcium influx consecutive to hypoxic injury. (26) Hence, the impediment of calcium channels can be a promising approach in tackling the rapid augmentation of Furin-activated organisms. Additionally, Li et al. stated in 2019 that Calcium Channel Blockers (CCB) play a novel role in halting the intensity of fever spikes episodes and the thrombocytopenic syndrome, categorized as manifestations of tick-borne hemorrhagic fever.(27)

Surprisingly, NO has been found to encourage calcium efflux from the cells leading to decreased intracellular calcium levels. This has been extensively studied in the context of the vasodilator action of NO. Van Hove et al. proved that NO stimulates Smooth Muscle Cells (SMCs) to relax directly and/or indirectly by removing the elevated calcium. (28)

This might signify that NO can inhibit Furin's action by decreasing cytosolic levels of calcium.

-Postexposure prophylaxis by inhaled NO

Argyropoulos et al. concluded that diagnostic viral load has no prognostic utility in terms of outcome prediction.(29) There are still conflicting data about this issue; Silva and colleagues in a more recent report, found the saliva viral loads to be significantly higher in patients with chronic respiratory conditions, cardiovascular conditions, kidney disease, and diseases that compromise the immune system. (30) Patients with four or more risk factors had much higher saliva viral loads than patients with fewer risk factors, as did male patients. However, there was no relation between nose and throat viral loads and the risk factors. Saliva viral loads were also higher in patients with worse clinical outcomes. This might signify that early interruption of viral replication in the upper respiratory tract might abort the development of significant symptoms and complications. This rationale might have led to the current inclusion criteria of the ongoing clinical trial for SaNOtize, which involves early administration of the intranasal medication within 48 hours of diagnosis. The administration of SaNOtize might extend later to medical personnel after a documented exposure to an infected case called post-exposure chemoprophylaxis.

Conclusion

While early reports of NO role in the treatment of COVID-19 suggested its use for the treatment of established ARDS, NO seems to have a much earlier and more efficient prophylactic role. It inhibits a protease needed for canonical viral replication of SARS-CoV-2, namely Furin, by decreasing calcium's cytosolic levels. This action can prevent the exponential increase of viral load in the upper respiratory tract leading to abortion of clinically symptomatic infection and subsequent complication. This might

add a significant tool for postexposure chemoprophylaxis in the at-risk group, especially medical personnel.

Figure 1 summarizes the antiviral effect of NO and its possible uses in the context of COVID-19

Declarations

Competing interests: The authors declare no competing interests.

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Table

Table 1: Review of in vivo and in vitro studies of the antiviral effect of Nitric Oxide

Reference number in text	Virus	Type of Nitric oxide Therapy	Study Model	Main outcome
4,5	SARS-CoV	NO donor, SNAP	In vitro	Inhibited SARS CoV replication cycle in a concentration-dependent manner(1)
		NO donors, SNAP & SNP	In vitro	SNAP &SNP inhibited the SARS CoV viral cytopathic effect(2)
17,18, 19	SARS-CoV-2	inhaled NO	multicenter randomized controlled trial	Ongoing, antiviral effect of high concentrations of inhaled NO administered during early phases of COVID-19 on spontaneous breathing patients, effect on disease progression.(3)
				Ongoing, testing inhaled Nitric Oxide in mechanically ventilated patients with severe acute respiratory syndrome in COVID-19 (SARS-CoV-2). (4)
			single center, randomized (1:1) controlled, parallel-arm clinical trial	Ongoing, prophylactic therapy to reduce the instance of COVID-19 disease in healthcare workers(4)
		SNAP	In vitro	SNAP delayed or completely prevented the development of viral cytopathic effect (5)
21	Coxsackievirus	NO donors SNAP	In vitro Murine model	NO inhibits CVB3 replication by inhibiting protease activity and interrupting the viral life cycle (6)
		iNO, SNAP		NO inhibits CVB3 replication in part by inhibiting viral RNA and protein synthesis (7)
		NO Donors SNAP, PFC, GTN, ISDN)		In vitro NO showed inhibition of the 2A proteinase activity CVB3-infected mice showed significantly reduced signs of myocarditis after treatment with GTN or ISDN (8)
22, 23	Influenza	Gaseous nitric oxide	In vitro	Viral NA inhibition by gNO was shown and may be responsible for

		(gNO)		this antiviral effect (9)
		SNAP		inhibition of influenza virus viral RNA synthesis (10)
24	Japanese encephalitis virus (JEV)	SNAP	In vitro	NO was found to profoundly inhibit viral RNA synthesis, viral protein accumulation, and virus release from infected cells(11)
		MDF to produce NO (inducible NO)	In vitro & Murine model	MDF stimulated macrophages inhibited virus replication with high levels of NO production. MDF treatment increased the survival rate of JEV infected mice(12)
13	Rhinovirus	Nitric Oxide donor (NONOate)	In vitro	(NONOate) inhibited both rhinovirus replication and cytokine production in a dose-dependent fashion without reducing levels of cytokine mRNA (13)
6	Reovirus	iNO	In vitro	Cytostatic effects antiviral effects e.g. reduction in DNA synthesis, protein synthesis & mitochondrial metabolism(14)
9	Dengue virus (DENV)	SNAP	In vitro	NO showed an inhibitory effect on viral RNA synthesis. The activity of the viral replicase was suppressed significantly (15)
10	Herpes simplex virus type 1 (HSV 1)			Nitric oxide had inhibitory effects on HSV1 protein and DNA synthesis as well as on cell replication (16)
20	Porcine circovirus type 2 (PCV2)	NO generated from (GSNO)	In vivo, In vitro (Murine model)	NO strongly inhibited PCV2 replication in vitro. NO reduced the progression of PCV2 infection in mice(17)
11	Crimean Congo hemorrhagic fever virus (CCHFV)	SNAP	In vitro	NO reduced virion progeny yield with reduction in expression of viral proteins; the nucleocapsid protein and the glycoprotein ,and vRNA(18)
12	Respiratory Syncytial Virus (RSV)	iNO , SNAP	In vitro	NO has significant direct antiviral activity against RSV, which is more potent with continuous, endogenous NO production than exogenous NO (19)
13	Human papillomaviruses (HPVs)	NVN1000, Topical NO-releasing polymer	In vitro	NO abrogated HPV-18 progeny virus production. Reduced HPV-18 E6 and E7 oncoproteins. Impaired S-phase progression and induced DNA damage in infected cultures (20)

14	Vesicular stomatitis virus (VSV)	iNO, SNAP	In vitro	anti-VSV effects of NO in form of significant inhibition of productive VSV infection (21)
15	Molluscum contagiosum	Topical acidified nitrite, nitric oxide liberating cream)	A double-blind, group-sequential clinical trial	75% cure rate in the active treatment group NO is effective therapy with 75% cure rate in treatment group compared to 21% in control group (22)
		topical SB206 (NO releasing topical gel)	multicenter, randomized, double-blind, vehicle-controlled clinical trial	SB206 is effective therapy with (SB206 12% / once daily) provided the best balance between MC lesion clearance and tolerability (22)
17	Hantavirus	iNO, SNAP	In vitro, murine model	NO strongly inhibited hantavirus replication in vitro. The viral titers in $iNOS^{-/-}$ mice were higher compared to the controls, suggesting that NO inhibits hantavirus replication *in vivo(23)*

Abbreviations: NO : Nirtic oxide, SNAP: S-nitroso-N-acetylpenicillamine, GTN: glyceryl trinitrate, ISDN: Isosorbide dinitrate, PFC: 4-phenyl-3-furoxancarbonitrile, iNO: inducible NO, CVB3: Coxsackievirus B3, gNO: Gaseous nitric oxide, NA: Neuraminidase, JEV: Japanese encephalitis virus, MDF: macrophage derived neutrophil chemotactic factor, NONOate: 3-(2-hydroxy-2-nitroso-1-propylhydrazino)-1-propanamine, HSV1 :herpes simplex virus type 1, DENV: Dengue virus, PCV2: porcine circovirus type 2, GSNO: S-nitrosoglutathione , CCHFV: Crimean Congo hemorrhagic fever virus, RSV: Respiratory Syncytial Virus, VSV: Vesicular stomatitis virus.

Figures

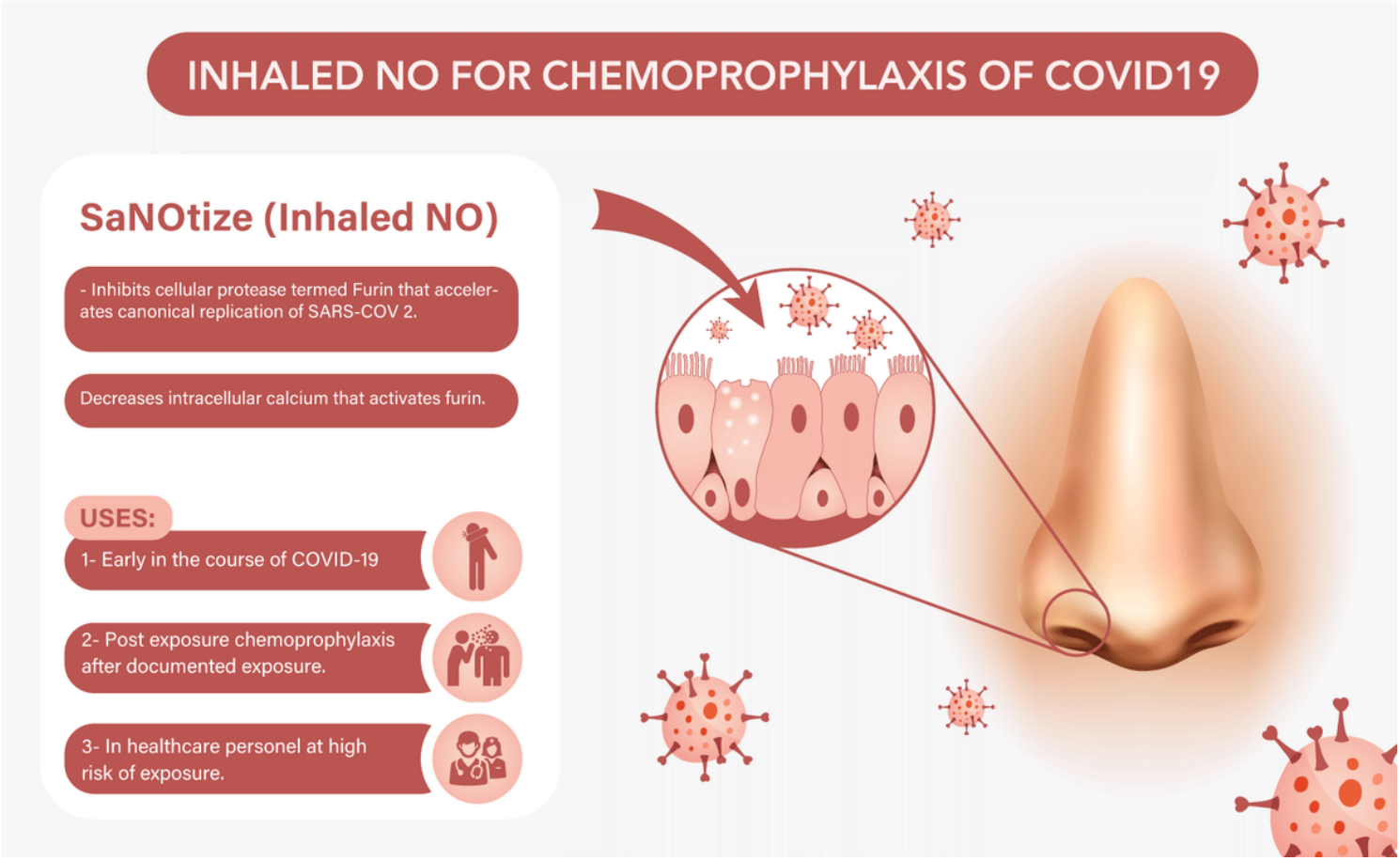

Figure 1

Title: Inhaled NO for chemoprophylaxis of COVID-19 Abbreviations: COVID-19: coronavirus 2019, NO, nitric oxide, SARS-CoV-2: Severe Acute respiratory syndrome coronaviridae-2