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LETTER TO THE EDITOR

Nicorandil a magic bullet or a *double edged sword* in critically ill COVID-19 patients?

Dear Editors,

We read with great interest the article by Ashour et al, where the authors have discussed the potential role of the anti-anginal drug nicorandil in managing sick COVID-19 patients with pulmonary and severe systemic inflammation, in the light of the pleotropic actions of this drug, especially its anti-inflammatory, anti-oxidant, antithrombotic and anti-fibrotic properties based on various experimental studies in animals.[1] Theoretically speaking this is an exciting option, worth exploiting in well carried out trials in COVID-19 patients given the protean properties of this drug. Somehow the authors have not anticipated and discussed a rare but very important and dangerous side effect of the drug which has occurred in actual patients in certain clinical settings, the deadly "potassium channel syndrome" with life-threatening refractory hyperkalemia which critically ill COVID-19 patients are potentially vulnerable to as well, a complication most intensivists, cardiologists and emergency physicians should be aware of. This cannot be overlooked and could actually wash away all the potential benefits mentioned by the authors regarding this drug when tried in critically ill patients with COVID-19.[2]

Nicorandil is a nitrate ester of nicotinamide developed as an anti-anginal drug, it possesses a dual mode of action, a nitrate-like cyclic GMP dependent properties and an agonistic action on the ATP-sensitive potassium (K^+ ATP) channels, dilating both venous and arterial vascular beds, respectively. Activation of potassium channels triggers dilatation of systemic and coronary arterioles. Besides the beneficial lowering of preload and afterload coronary blood flow is enhanced as well.[3]

ATP sensitive potassium (K^+ATP) channels constitute a link between the metabolic and energetic state of cells due to their sensitivity to ATP and ADP concentrations. K^+ATP channels have been discovered and elucidated in multiple tissues and organs of the body including heart, pancreas, vascular smooth muscles, skeletal muscles and ocular tissue. There are several tissue specific subtypes of K^+ATP channels, each with their own unique set of functions and response to pharmacological modulation (potassium channel openers and blockers).[4] This has paved way for considering the potential extra cardiac uses of nicorandil in ophthalmology for glaucoma and ischaemic retinopathy etc. in the future, based on tissue specific functions of KATP channels.[5] In vascular smooth muscle cell, the K^+ATP channels help in regulating blood flow and play an important role in meditating systemic vasodilation during sepsis, hypotension, hypoxia, and acidosis, thus maintaining blood flow and enhancing tissue perfusion, but contrarily it causes vasopressor refractory hypotension during extreme activation of K^+ ATP channels.[6] Nicorandil induced K^+ ATP activation causes extrusion of potassium ions into extracellular fluid inducing membrane hyperpolarization which leads to closure of voltage gated calcium channels and hence vasodilation. This mechanism on the one hand accounts for its anti-anginal properties but on the other hand can cause life-threatening refractory hyperkalemia in certain clinical situations which are associated with K^+ ATP channel activation, like cardio-respiratory decompensation, sepsis, hypotension, hypercarbia and acidosis leading to excessive venting of potassium from already upregulated K^+ channels causing its overwhelming distribution into the ECF. Singer coined the term "potassium channel syndrome" and since then a few cases of nicorandil-associated potassium channel syndrome with refractory hyperkalemia have been reported in the literature (our experience too, unpublished data).[7–9] Nicorandil-associated hyperkalemia is resistant to conventional antikalemic measures and responds to withdrawal of the drug and introduction of a potassium channel blocker glibenclamide.[10]

Critical illness is known to potentiate the potassium channel opening capacity of this drug, sick COVID-19 patients have a perfect setting for this since respiratory decompensation, hypoxia, acidosis, renal dysfunction and hypotension are invariably present in them. Given the setting of an acute illness especially associated with SIRS like picture, the risk of hyperkalemia with nicorandil is very high since multiple players operate synergistically to cause activation of potassium channels with the added influence of the drug in sustaining that state of K^+ATP channel activation and its deadly consequences. In SIRS and sepsis since K^+ ATP channels are already upregulated, experts have even considered the need for novel potassium channel blockers to mitigate hypotension. Therefore, theoretically speaking even if nicorandil is to be used in critically ill COVID-19 patients as suggested by the authors, higher doses and intravenous infusions would possibly be required to offset the inflammatory and thrombotic cascades which would mean a higher risk of life-threatening hyperkalemia.

Just based on a few in vitro experimental studies and translating them into the immediate clinical use of nicorandil for blunting the complex inflammatory onslaught and an overwhelming thrombosis and lung fibrosis in critically ill COVID-19 patients could be detrimental. Its anti-inflammatory, antithrombotic and antifibrotic benefits could be far outweighed by its predominant pharmacological

action of K^+ ATP channel activation which could set into motion a perpetual activation of the already upregulated potassium ATP channels due to the viral syndrome and its complications, triggering a life-threatening "hyperkalemic storm" amidst a cytokine storm.

The rapid evolution and dissemination of the COVID-19 pandemic has challenged the systematic and structured scientific approach to drug/vaccine development. This unprecedented situation, has led to dissemination of anomalous measures impelling scientists and clinicians for an urgent need of a rapid therapeutic response amidst a major global crisis, pushing the medical fraternity to the use of off-label drugs like never before which is justified given the magnitude of the pandemic. Besides a successful vaccine which would warrant a time frame to prove its safety and efficacy, an effective pharmacological anti-viral agent is badly needed to bridge the gap with the vaccine development and use. A magic bullet is required given the very complex pathophysiology of COVID-19 infection.

Importantly, while considering the actions and benefits for the potential indication of any drug equal attention and weight should be given to its side effect profile too (hydroxychloroquine and azithromycin in COVID-19 are examples). So we conclude by saying that at this point in time we would respectfully disagree with the authors' hypothesis for considering the potential use of nicorandil as a magic bullet in critically ill COVID-19 patients which we feel would not be without life-threatening risks unless proven otherwise in well-designed studies.

KEYWORDS

COVID-19 pandemic, nicorandil, pleotropic action, potassium ATP channels, potassium channel syndrome

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR CONTRIBUTION

THM conceptualized and wrote the draft and reviewed and approved the final version. PZ contributed in writing of the draft. BJ collected the references and made fine alterations in the manuscript. AZ collected the references.

DATA AVAILABILITY STATEMENT

This manuscript encourages data sharing. It is a letter in response to an article published and the supporting data is taken from the references attached.

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