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COMMENTARY

COVID-19 and NSAIDS: A Narrative Review of Knowns and Unknowns

Joseph V. Pergolizzi Jr · Giustino Varrassi · Peter Magnusson · Jo Ann LeQuang · Antonella Paladini · Robert Taylor · Charles Wollmuth · Frank Breve · Paul Christo

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ABSTRACT

Concern about the appropriate role of nonsteroidal anti-inflammatory drugs (NSAIDs) in COVID-19 speculate that NSAIDs, in particular ibuprofen, may upregulate the entry point for the virus, the angiotensin-converting enzyme (ACE) 2 receptors and increase susceptibility to the virus or worsen symptoms in existing disease. Adverse outcomes with COVID-19 have been linked to cytokine storm but the most effective way to address exaggerated inflammatory response is complex and unclear. The Expert Working Group on the Commission of Human Medicines in the UK and other organizations have stated that there is insufficient evidence to establish a link between ibuprofen and susceptibility to or exacerbation of COVID-19. NSAID use must also be categorized by whether the drugs are relatively low-dose over-the-counter oral products taken occasionally versus higher-dose or parenteral NSAIDs. Even if evidence emerged arguing for or against NSAIDs in this setting, it is unclear if this evidence would apply to all NSAIDs at all doses in all dosing regimens. Paracetamol (acetaminophen) has been proposed as an alternative to NSAIDs but there are issues with liver toxicity at high doses. There are clearly COVID-19 cases where NSAIDs should not be used, but there is no strong evidence that NSAIDs must be avoided in all patients with COVID-19; clinicians must weigh these choices on an individual basis.

Keywords: Acetaminophen; COVID-19; Ibuprofen; NSAIDs; Paracetamol; SARS-nCoV-2 virus

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J. V. Pergolizzi Jr · J. A. LeQuang (✉) · R. Taylor · C. Wollmuth · F. Breve
NEMA Research, Inc, Naples, FL, USA
e-mail: joannlequang@gmail.com

G. Varrassi
Paolo Procacci Foundation, Rome, Italy

G. Varrassi
World Institute of Pain, Los Angeles, USA

P. Magnusson
Centre for Research and Development, Uppsala/Gävleborg County, Gävle, Sweden

P. Magnusson
Department of Medicine, Cardiology Research Unit, Karolinska Institutet, Stockholm, Sweden

A. Paladini
Department MESVA, University of L'Aquila, L'Aquila, Italy

F. Breve
Department of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, PA, USA

P. Christo
The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Key Summary Points

Confusion has arisen over whether use of NSAIDs may increase the likelihood of contracting COVID-19 and/or if NSAIDs may exacerbate symptoms in people with COVID-19.

Hyperactive inflammatory response called "cytokine storm" can occur with COVID-19 and plays a major role in negative outcomes, but the role of anti-inflammatories, such as (but not limited to) NSAIDs, is unclear.

To date, there is no strong evidence pro or con for the use of NSAIDs in a person diagnosed with COVID-19.

Oral NSAIDs used briefly during a mild episode of COVID-19 are not necessarily comparable to round-the-clock parenteral NSAID administration in a critical patient.

Acetaminophen (paracetamol) may be administered to patients with COVID-19 but caution must be observed with dosing.

INTRODUCTION

Concern about the role of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19 has led to considerable speculation. Fang et al. offered an early commentary on COVID-19 that suggested that angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) may be associated with worse COVID-19 outcomes and added that ibuprofen may be associated with upregulation of the ACE2 receptors, the presumptive entry point of the SARS-CoV-2 virus [1, 2]. Further, immune suppression may occur with some NSAIDs [2], such as, but not limited to, ibuprofen. However, Fang and colleagues subsequently cautioned against "overinterpretation" of these hypotheses that in some cases led to abrupt changes in drug regimens; they state that ACE inhibitors and NSAIDs are important therapeutic drugs and should not be discontinued without careful clinical judgement [2]. Likewise, a website run by prominent international specialists entitled *ACE2 and Hypertension* advises individuals taking ACE inhibitors or ARBs not to change their drug therapy unless a physician advises them to do so [3].

The speculation about NSAIDs for patients with COVID-19 is twofold: first, do NSAIDs increase the likelihood that a person will contract COVID-19 and, second, will a patient with COVID-19 taking NSAIDs have exacerbated symptoms? There is no evidence that either of these is the case [4], but there have been observations that worse outcomes in COVID-19 may be associated with NSAID use. In this connection, it must be pointed out that worse outcomes with COVID-19 typically occur in older patients, and the elderly are more likely than younger patients to take NSAIDs for chronic pain and are also at elevated risk for COVID-19 complications [5]. No age-adjusted reports of the association between adverse COVID-19 outcomes and NSAID use have been published to the best of the knowledge of the authors. Thus, older age and higher rates of comorbid conditions may be confounding factors.

The purpose of this article is to provide a brief overview of what is currently known—and what is not known—about the use of NSAIDs in the setting of COVID-19.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

COVID-19 PROGRESSION AND THE INFLAMMATORY CASCADE

Siddiqi and Mehra have staged the progression of COVID-19 on the basis of 72,314 cases observed in China and identified three stages. Stage I is mild disease and represents the majority of infections; stage II is moderate disease with pulmonary involvement with or without hypoxia; and stage III is severe illness

characterized by extrapulmonary hyperinflammation, in particular observed by biomarkers such as interleukin (IL)-2, IL-6, IL-7, granulocyte colony-stimulating factor (GCSF), macrophage inflammatory protein 1-alpha (MIP1α), C-reactive protein (CRP), ferritin, and high D-dimer scores [6]. Prior to the outbreak of COVID-19, the association of intense cytokine activity with adverse outcomes of influenza had been reported [7]. The severity of influenza results from the interplay of viral virulence and host resistance. In mild cases of flu, the host has a degree of resistance such that the disruptions to homeostasis are quickly resolved and normal balance is restored. When that resistance is hyperactive, an exaggerated inflammatory response may occur called "cytokine storm."

Cytokine storm can cause injury to tissue, morbidity, and mortality [8]. The SARS-nCoV-2 virus targets epithelial cells of the respiratory system and these progeny viruses can replicate to infect other cells, producing an inflammatory response when those cells die either by necrosis or apoptosis [9]. High levels of pro-inflammatory cytokines and CRP have been observed in critically ill patients with COVID-19 [10]. Cytokine storm has likewise been observed in patients with infectious and rheumatic diseases, usually arising from the focal point of the infection and spreading outward through the circulatory system [10]. In diseases associated with coronaviruses, such as Middle Eastern respiratory syndrome (MERS) or severe acute respiratory syndrome (SARS), the marked increase in inflammatory cytokines parallels a rapid replication of the virus resulting in lung injury and potentially life-threatening acute respiratory distress syndrome (ARDS) [10]. Early evaluations of patients with COVID-19 suggest similarly high levels of pro-inflammatory cytokines along the lines of MERS and SARS [10]. In China, one of the diagnostic criteria for COVID-19 is lymphocytopenia [10]. Patients with COVID-19 have reduced levels of T cells and natural killer (NK) cells and some critically ill patients with COVID-19 had undetectable levels of NK cells [10]. It has been speculated that cytokine storm destroys lymphocytes, and destruction of secondary lymphoid tissue has been observed on autopsy of patients with COVID-19 [10].

As cytokine storm likely plays a major role in adverse outcomes of severely ill patients with COVID-19, the role of anti-inflammatories ranging from NSAIDs to glucocorticoids to hydroxychloroquine and others would seem beneficial in an effort to reduce inflammation before it overwhelms the body's systems. Tocilizumab, an IL-6 inhibitor, has also been discussed in this context along with anakinra (an IL-1RA) to suppress cytokine storm [6, 10]. TNFα blockade via the etanercept receptor downregulates inflammatory response in cytokine storm and etanercept has been proposed as a potential pharmacological strategy in controlling influenza-induced viral pneumonia [11]. In a study of mice infected with the influenza A/H5N1 virus, treating them with celecoxib plus mesalazine plus zanamivir significantly reduced cytokine dysregulation and prevented apoptosis to a greater extent than mesalazine or zanamivir alone [12]. That is, the addition of celecoxib plus other drugs reduced mortality in these infected mice. While such treatment may have value to address the patient's hyperinflammatory state, it must be recognized that the prognosis for patients with stage III COVID-19 is poor.

ANTI-INFLAMMATORY THERAPY FOR INFLUENZA

Anti-inflammatory therapy for influenza may be associated with certain drawbacks. The use of an anti-inflammatory might potentially slow viral elimination and elevate the risk of a secondary infection. While an anti-inflammatory can reduce inflammation, it may have a limited or poorly understood effect on cytokine storm, which involves multiple cytokines and complex interactions. In other words, an anti-inflammatory agent may affect certain cytokines but not others [10]. Even if anti-inflammatory therapy were to be advocated, it is not yet clear which therapies are best, at which point during the disease, at what doses, and for what duration.

Of course, the role of NSAIDs in viral infections of other kinds has been controversial [13]. One argument against the use of NSAIDs and acetaminophen is that these are antipyretic drugs that may mask a rising fever associated with COVID-19 and thus delay diagnosis and rapid management of the infection [14]. Selective coxibs have been associated with an increased cardiovascular risk, but the risk varies with the particular drug [15–17]. Since COX-2 is associated with prostaglandin I_2 (PGI_2 or prostacyclin), NSAIDs that inhibit COX-2 reduce PGI2 but do not inhibit the prothrombotic platelet thromboxane A_2 production, resulting in a selective reduction in prostacyclin activity that may set the stage for endothelial damage [18, 19]. NSAIDs suppress the production of prostaglandins, lipids that are associated with fever and pain. Ibuprofen, a widely used NSAID, is not strongly selective and blocks both COX-1 and COX-2 [13, 20]. In cases of multiple organ failure, which has happened with SARS, MERS, and possibly COVID-19, the use of NSAIDs might more easily be associated with gastrointestinal damage. If gastrointestinal symptoms occur, this should be carefully investigated and treated [21].

Prostaglandin E_2 is associated with the classic symptoms of inflammation such as fever, redness, and localized edema [22]. The confusion about NSAIDs arises mainly because prostaglandin production is complex and can both promote and inhibit inflammatory processes. The NSAID indomethacin is known to block the RNA synthesis of viruses, but this mechanism is independent of COX inhibition and it is not clear if this antiviral activity applies to the SARS-nCoV-2 virus [22].

NSAID RISKS

NSAIDs may be contraindicated in some patients with respiratory disorders. NSAIDs administered to patients with an acute respiratory infection have been implicated in acute myocardial infarction (adjusted odds ratio 3.41, 95% confidence interval, 2.8–4.2) but it must be noted that patients with acute respiratory infection have an adjusted odds ratio of 2.65 (95% confidence interval, 2.3–3.1) for acute myocardial infarction even without NSAID use [23]. The risk was much higher with parenteral than oral NSAID use (adjusted odds ratio 7.22, 95% confidence interval, 4.1–12.8) [23]. A similar increased risk for stroke was observed in patients suffering acute respiratory infection and taking NSAIDs, in particular, by parenteral route. NSAIDs may alter the intrinsic function of neutrophils and, in that way, change bacterial clearance and delay the resolution of the inflammatory process [24].

CLINICAL CONSIDERATIONS

To date there is no strong evidence in favor or disputing the use of NSAIDs in patients diagnosed with COVID-19 [4, 25]. The Expert Working Group of the Commission on Human Medicines in the UK has issued a statement that there is "currently insufficient evidence to establish a link between the use of ibuprofen and susceptibility to contracting COVID-19 or the worsening of its symptoms" [26]. Indeed, any blanket "for" or "against" statement on this topic would not be clinically realistic. For COVID-19, oral NSAIDs might only be used intermittently over a very short period of time, and it is not clear if this would be the same as chronic, round-the-clock NSAID therapy or parenteral NSAID administration [25]. Since NSAIDs are available over-the-counter, accurate records about who has taken them, when, and in what doses is often sparse and, if collected from patient memory, would be inherently unreliable. Furthermore, even if evidence emerged favoring or rejecting one particular NSAID in this setting, it is not clear whether such evidence would apply to all NSAIDs in similar fashion.

As COVID-19 ravages the globe, clinicians, scientists, epidemiologists, regulators, and politicians are eager to offer sane, sound advice to keep people safe. Unfortunately, our social-media-driven era of nonstop news is not compatible with the slow and serious work of science. Clinicians are being confronted with hypotheses, speculation, anecdotal reports, and conjecture on important topics such as the use

of NSAIDs in patients with COVID-19 with little strong evidence to guide them. First, clinicians must consider who is taking the NSAID and why. There is no evidence that the occasional use of an oral, over-the-counter NSAID for a few days by a person with suspected or diagnosed mild COVID-19 infection will exacerbate the infection. Second, there is no reason to think that patients taking prescribed NSAIDs for a chronic painful condition should stop taking this drug for fear it might increase their risk of contracting COVID-19 or exacerbate it if they get it [5]. It is likely that many patients with mild cases of COVID-19 may take an over-the-counter remedy to help manage symptoms such as muscle aches and fever. Acetaminophen (paracetamol) has been proposed as an alternative to NSAID use, but there are also issues with acetaminophen toxicity [27].

To be sure, there are COVID-19 cases when NSAIDs should not be used. But there is no strong evidence that they must be avoided in all patients with COVID-19. Clinicians on the frontlines and those advising patients with mild COVID-19 cases managed at home should weigh these considerations carefully.

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