

SYNOPSIS

April 3, 2020

COVID-19 What We Know So Far About... Use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Introduction

“What We Know So Far” documents are intended to provide an overview of some of the published and unpublished reports related to emerging issues with respect to coronavirus disease 2019 (COVID-19). The reports are found through ongoing scanning of the published literature and scientific grey literature (e.g., [ProMed](#), [CIDRAP](#), [Johns Hopkins Situation Reports](#)), as well as media reports. It is recognized that there may be additional information not captured in this document. As this is a rapidly evolving outbreak, the information will only be current as of the date the document was written.

Key Messages

- Concerns have been raised about the safety of using Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen (Advil® or Motrin®) or naproxen (Aleve®) in patients with COVID-19 infection.
- There is insufficient scientific evidence at this time to routinely avoid NSAIDs in patients with COVID-19.
- Acetaminophen (Tylenol®) is not an NSAID and continues to be a preferred, first-line medication for symptom management due to similar efficacy and reduced toxicity.

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen (Advil® or Motrin®) are commonly used to relieve fever and symptoms of viral infections, such as influenza. However, because NSAIDs inhibit the production of prostaglandins, substances that modulate inflammation and the immune system, there is some concern that NSAIDs could mask infectious symptoms or reduce the body’s immune response to infection in general. Use of ibuprofen could also potentially increase the upregulation of ACE2 receptors, which theoretically could worsen COVID-19 by increasing viral entry into human cells.¹

Recent statements in the media have highlighted a potential concern with using anti-inflammatory agents, particularly NSAIDs in patients infected with COVID-19. These concerns escalated on March 14,

when the French government released a report stating “serious adverse events” may be associated with NSAIDs in people with COVID-19.² Subsequently, a [Tweet](#)³ by France’s Health Minister Dr. Olivier Véran, with the following statement was circulated:

“The taking of anti-inflammatories [ibuprofen, cortisone ...] could be a factor in aggravating the infection. In case of fever, take paracetamol (acetaminophen). If you are already taking anti-inflammatory drugs, ask your doctor’s advice.”

On March 17, a public health official from the World Health Organization (WHO) supported this recommendation while awaiting further guidance:⁴

“...we recommend using rather paracetamol (acetaminophen), and do not use ibuprofen as a self-medication”

However, on March 18 the WHO reversed its position, indicating in a [Tweet](#)⁵ that the organization does not recommend against ibuprofen as there is currently no published clinical or population-based data on this topic. Health Canada has echoed these statements, indicating there is insufficient scientific evidence to support these concerns.⁶

The following document summarizes the available evidence on whether NSAIDs should be avoided in patients with suspected or laboratory-confirmed COVID-19 infection.

Relevant Literature

- There is currently no safety or efficacy data regarding the use of NSAIDs (e.g., ibuprofen) or acetaminophen specifically in patients infected with SARS CoV-2, the virus causing COVID-19.
- Concerns about ibuprofen seem to have originated from statements by a physician in southwest France who indicated that four young patients infected with COVID-19 with no underlying comorbidities went on to develop severe illness after using NSAIDs to treat early symptoms of the disease. This report was based on anecdotal evidence and at the time of this review, has not been published.⁷
- Some clinicians cite drug safety reports and trials that indicate there may be differences between acetaminophen and ibuprofen in terms of infection outcomes. One study comparing ibuprofen, acetaminophen and steam inhalation for respiratory tract infections (not including COVID-19) in primary care found no benefit to ibuprofen in symptom resolution, but a significant increase in return visits for new infections within 28 days (12% acetaminophen vs. 20% ibuprofen). The authors caution that this finding may be due to chance, but indicate that there may be a biological mechanism explaining this association given ibuprofen’s potential role in modifying the immune response.⁸
- However, a large systematic review and meta-analysis comparing acetaminophen to ibuprofen in over 30,000 pediatric patients with fever or pain found no difference in overall harm.⁹
- On the other hand, some specific NSAIDs such as naproxen and indomethacin may actually have anti-viral activity. Naproxen binds to nucleoproteins of influenza A and B and as a result exhibits antiviral activity.¹⁰⁻¹¹ Indomethacin has been shown to have in vitro and in vivo activity against SARS Co-V in animal models.¹²

- Acetaminophen and NSAIDs are generally well-tolerated when used for short term management of pain or fever, however it is known that NSAIDs are associated with a greater risk of dose-related, cumulative side effects particularly in older adults¹³, including gastrointestinal ulceration, kidney injury and fluid retention.¹⁴ In addition, NSAIDs should also be generally avoided in individuals with hypertension, cardiovascular and renal disease.¹⁵
- Corticosteroids are not NSAIDs but also have an inflammatory mechanism of action. The WHO Interim Guidance on the Clinical Management of SARS-CoV 2 recommends against the routine use of systemic corticosteroids for COVID-19 related viral pneumonia or acute respiratory distress syndrome (ARDS) unless initiated for a different indication.¹⁶

Summary

- There is currently insufficient evidence to avoid NSAIDs in patients with COVID-19 infection. Acetaminophen (Tylenol®) continues to be a preferred first-line medication for symptom management due to the lower potential for side effects. If acetaminophen is not appropriate, then the usual risks and benefits of using NSAIDs should be considered based on an individual patient's comorbidities and risk factors.
- Patients with or without COVID-19 infection who regularly take anti-inflammatory agents such as NSAIDs (e.g., ASA or acetylsalicylic acid, Aspirin®) or corticosteroids (e.g., prednisone) for management of chronic conditions should continue on these medications unless otherwise advised by their healthcare professional. Abruptly discontinuing these medications may result in harm.

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