

Title	Summary of evidence: Use of non-steroidal anti-inflammatory drugs (NSAID) in Covid-19 patients.
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Requesting area	COVID-191. Keralty Public Health Crisis Committee
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Question 1:

Is the use of NSAID (Ibuprofen) indicated in the treatment of confirmed patients with COVID-19 infection?

Methodology:

A fast-systematic search was performed. (Fast Systematic Search Manual. Institute of Clinical Global Excellence. 2019)

Terms of search: COVID 19, Non-Steroidal Anti-inflammatory Drugs.

Types of studies: Clinical practice guidelines, systematic reviews, meta-analysis, clinical trials and other primary studies.

Source of information: Medline and Scopus

Background: French healthcare professionals suggest that there is evidence of severe adverse effects with the use of NSAID, such as ibuprofen, in patients with COVID-19 infection and recommend treatment with acetaminophen. It seems that these comments came from reports of the experience of use of this medication in southwest France. These groups report 4 cases of young, previously healthy patients, with COVID-19 infection who developed severe symptoms after using non-steroidal anti-inflammatory drugs (NSAID) during the initial phase of their disease. This situation has generated doubts about the role of the NSAID in the treatment of the patients with COVID-19 infection and a large amount of different positions in scientific and general dissemination journals.

1. Jean-Louis Montastruc, clinical pharmacology professor in Central Toulouse University Hospital: "these NSAID harmful effects are not a surprise, since 2019, with the advice of National Agency for the Security of Drug and Health Products, it has been said to the French health professionals not to treat fever or infections with ibuprofen."
2. In the United Kingdom, Paul Little, primary care research professor of Southampton University, states, "The general feeling is that the French advice is pretty reasonable. Now a days, there is a considerable amount of case control studies in literature in different countries, that report an increase of the duration of the disease and its association with septic and cardiovascular complications. These complications can be more frequent when non-steroidal anti-inflammatory drugs are used."

3. Ian Jones, virology professor in Reading University, states, “the anti-inflammatory properties of ibuprofen could “dampen” the immunitary system, this could delay the recuperation process. He adds that due to similarities between the new virus (SARS-CoV-2) and the SARS I, the COVID-19 is implicated with the angiotensin converting enzyme, this enzyme regulates the salt and water concentration in the blood and could contribute to pneumonia.
4. Dr. Rupert Beale, cellular biology group leader in the Crick Francis Institute said, “There are good reasons to avoid the ibuprofen, this medication could increase the acute renal lesion caused by any serious disease, including the severe Covid-19 disease.

Summary of evidence: The conducted search did not find any evidence about the specific use of ibuprofen in patients with COVID-19, and as the Agencia Española del Medicamento states, “there is no data that associates the use of NSAID with the worsening of the COVID-19 infection.”

Nevertheless, indirect evidence derived from clinical studies is available:

1. Controlled randomized study, open factorial parallel group. This study evaluated the analgesia and vapor inhalation strategies for respiratory tract infections in patients older than 3 years of age with acute respiratory tract infections treated for in primary care in the United Kingdom. They found that the patients with respiratory infections and symptoms like cough, a cold or odynophagia who received a prescription for ibuprofen instead of paracetamol by their primary physician, had a higher chance of suffering diseases or severe complications (2).
2. Prospective cohort study that evaluates if the exposition to NSAID in community acquired pneumonia (CAP) patients before being admitted to de hospital was associated with the development of pleural complications or pulmonary abscess. In the multivariable analysis two factors were associated independently with the development of pleuro parenquimatose complications: NSAID intake (Odds Ratio (OR)= 2.57 (1.02-6.64); p= 0.049) and alcohol abuse (OR=2.68 (1.27-5.69); p=0.01). This suggests that the use of NSAID in young healthy patients may worsen the course of CAP, delaying the start of treatment and the generation of an increase in the rate of pleuropulmonary complications.

At this moment, it is being evaluated for the whole European Union; if there is any relation between the use of ibuprofen and the worsening of the COVID-19 infection.

Recommendations:

1. At this moment there is no available data that supports the association between ibuprofen and the worsening of COVID-19 infection, nevertheless, there is indirect evidence that the use of NSAID can delay the identification of symptoms and can be associated with complications in patients with respiratory infection or CAP.
2. It has been described that ibuprofen may mask symptoms in other infections and this can delay the diagnosis.

3. The security profile (renal, liver, gastrointestinal, cardiovascular) is vital when choosing the symptomatic treatment for this infection.
4. The European Union is evaluating this signal in the COVID-19 infection. Results are to be available by May 2020 (4).
5. At the moment, there is no solid proof that ibuprofen may worsen in the context of COVID-19 infection. Despite this, until there is no more information available, the patients should take paracetamol or acetaminophen to treat the coronavirus symptoms, unless the physician states any contraindication.

Patient recommendations:

1. The use of paracetamol or acetaminophen are recommended preferably in order to treat symptoms associated with the COVID-19 infection. The dosage should be indicated by your physician.
2. The use of NSAID (for example: ibuprofen, diclofenac, naproxen) are not recommended, due to the secondary renal and gastrointestinal effects, especially in patients with risk factors.

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