The use of nonsteroidal anti-inflammatory drugs by COVID-19 patients – in a nutshell

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Abstract

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a large scale of morbidities and mortalities worldwide, posing a significant threat to global health. COVID-19 has been challenging due to a lack of established treatment guidelines. Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise of a heterogeneous group of compounds used for the symptomatic relief of fever, pain and inflammation. NSAIDs exert their effects by inhibiting prostaglandins' biosynthesis, resulting in anti-inflammatory, analgesic, and antipyretic effects. They may be beneficial in reducing inflammation and prevent fatal cytokine storms in COVID-19. However, the use of NSAIDs by COVID-19 patients has been controversial, with some reports recommending their use, while others contraindicated them. This may be due to the heterogeneous nature of COVID-19 including different strains or cases. There seem to be COVID-19 cases where NSAIDs should not be used; however, there is no evidence that NSAIDs should be avoided in all COVID-19 patients.

Keywords: nonsteroidal anti-inflammatory drugs, NSAIDs, COVID-19, coronavirus, inflammation, pain, ibuprofen, diclofenac, aspirin, naproxen, indomethacin, paracetamol

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Introduction

Coronaviruses are a family of enveloped, positive-sense single-stranded RNA viruses belonging to the family Coronaviridae that was first described in the 1960s.[1,2] Although they were first described in the 1960s, coronaviruses have only recently been discovered to infect humans.[3] Coronaviruses (CoV) are now known to cause a range of human respiratory tract infections varying from mild cold to severe respiratory distress syndrome.[4] The novel CoV disease, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for the current coronavirus disease (COVID-19), which causes large-scale morbidities and mortalities worldwide.[5] SARS-CoV-2 was identified as the seventh type of coronavirus to infect humans.[6]

SARS-CoV-2 infection is highly heterogeneous, ranging from asymptomatic infection to mild, moderate, or severe COVID-19. The most common symptoms of COVID-19 are fever, dry cough, sore throat, headache, fatigue, muscle pain, dyspnoea, anosmia, and ageusia.[5,7] COVID-19 is known to cause a spectrum of respiratory conditions differing in severity, including mild upper respiratory tract complications, acute respiratory distress syndrome (ARDS), and pneumonia in more deleterious cases.[7] Severe COVID-19 is frequently characterised by pulmonary hyper-inflammation. In extreme cases, patients experience a dramatic increase in the levels of pro-inflammatory chemokines and cytokines, including interleukin 6 (IL-6), and tumour necrosis alpha (TNF-α), a condition known as "cytokine storm".[5] This leads to the development of ARDS, septic shock, metabolic acidosis, coagulation dysfunction, and even death. Currently, there is no effective treatment plan for COVID-19, but various approaches are being tried depending upon various signs and symptoms of individual patients.[5] In addition, there is no agreement on its supportive treatment protocol.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically heterogeneous group of compounds that have long been used to manage respiratory infections, control fever, reduce chest pain, and cough.[8] NSAIDs are defined as inhibitors of cyclooxygenase (COX) enzymes (COX-1 and COX-2), which metabolise phospholipid derived arachidonic acid (AA) to prostanoids. Prostanoids are a subclass of eicosanoids consisting of prostaglandins (PGs), thromboxanes, and prostacyclins, all of which are inflammatory mediators. Thus, PGs are the end products of fatty acid metabolism and are produced via the COX pathway.[9] COX-1 enzymes are constitutively expressed in the body and are involved in homeostatic functions, including those related to the gastrointestinal mucosa lining, kidney function, and platelet aggregation.[10] COX-2 enzymes are mainly expressed at inflammatory sites and are involved in processes that lead to vasodilation, increased vascular permeability, and leukocyte chemotaxis. NSAIDs are extensively used for the treatment of pain and inflammation, including patients with chronic inflammatory conditions such as arthritis and osteoarthritis.[9] NSAIDs are classified into two types, i.e. traditional non-selective NSAIDs that inhibit both COX-1 and COX-2; and selective NSAIDs that exclusively inhibit either COX-1 or COX-2 enzymes.[10] Several NSAIDs compounds are available, with the most common being ibuprofen, diclofenac, aspirin, naproxen, indomethacin, and paracetamol.[8]

Mechanisms of action of NSAIDs

NSAIDs exert their effects by inhibiting the biosynthesis of PGs, resulting in anti-inflammatory, analgesic, and antipyretic effects.[11] PGs are potent eicosanoid lipid mediators made at sites of tissue damage or infection that mediate inflammation. As previously mentioned, PGs are end products of fatty acid metabolism, synthesised through the COX pathway.[9] In order to understand the mechanisms of actions of NSAIDs, it is better to first understand the biosynthesis of PGs. The biosynthesis of PGs occurs in three steps starting with the mobilisation of AA from the membrane phospholipids through the action of phospholipase A2 enzyme.[9] The AA is an unsaturated 20-carbon fatty acid embedded in cell membranes as a phospholipid ester, which serves as the precursor for PG synthesis.[12] This is followed by the biotransformation of the free AA by COX enzymes into PG endoperoxidases, PGG2, and PGH2.[13] PGH2 is the precursor of the biologically active PGs and thromboxanes. PGH2 is then isomerised into various prostanoids such as thromboxane A2 (TXA2), prostacyclin (PGI2), PGD2, PGE2, and PGF2a.[13] Prostanoids play a key role in the generation of the inflammatory process. In addition, TXA2 is a potent vasoconstrictor and a stimulator of platelet aggregation.[14] Prostacyclin is expressed in the vascular endothelium and inhibits platelet aggregation, while PGE2 and PGI are potent vasodilators that account for increased blood flow in inflamed tissues.[14]

NSAIDs mainly produce their effects by inhibiting the biosynthesis of PGs. NSAIDs exert their anti-inflammatory effects by inhibiting prostaglandin G/H synthase, or COX enzymes.[11] NSAIDs are classified as mild analgesics, as they also alleviate pain mediated by inflammation. They act as anti-inflammatory and analgesic agents by inhibiting COX-2 dependent PGs in cells at an in-flammatory site and in the spinal cord.[18] They also exert their analgesic effect by decreasing the production of PGs that sensitise nociceptors to bradykinin. In addition, NSAIDs exert their antipyretic effects by inhibiting the synthesis of PGE2.[11] PGE2 is responsible for triggering the hypothalamus to increase body temperature during inflammation. Thus, PGE2 inhibition lowers body temperature. It has been suggested that COX inhibition may not be the only anti-inflammatory mechanism of action of NSAIDs.[15] However, other mechanisms are not well defined.

Indications

NSAIDs have a wide range of indications, especially in cases where pain and inflammation are present.[13,16] The most common indications of NSAIDs include mild to moderate pain due to inflammation and tissue injury, including fractures, sprains, and soft tissue injury; osteoarthritis and rheumatoid arthritis; acute gout; antipyretic; and postoperative pain.[13] NSAIDs are also useful in the treatment of dental pain, dysmenorrhea, as well as headaches and migraines.[13] They also have potential use in COVID-19.

Dosage

NSAIDs are prescribed in different doses depending on the condition, or the type of NSAIDs. The most preferred route of administration of NSAIDs is oral, unless the patient is vomiting or comatose. NSAIDs are administered regularly at a fixed dose at appropriate time intervals, reviewed and adjusted according to the type and severity of pain and inflammation. Ibuprofen is administered orally with a recommended daily dosage of 200–400 mg every 4–6 hours to a maximum of 1 200 mg/day (Table I).[17] When administered orally, the recommended daily dose of diclofenac is 25–50 mg every 8–12 hours, to a maximum dosage of 150 mg/day. However, when administered intramuscularly, the recommended daily dose of diclofenac is 75 mg every 12 hours, to a maximum of 150 mg/day for two days only. The recommended oral dose of aspirin is 350–1 000 mg every 4–6 hours to a maximum dosage of 4 g per day. Naproxen oral dosage of 250–500 mg every 6–12 hours with a maximum of 1 500 mg per day is recommended. Indomethacin is administered orally and a dose of 25–50 mg every 6–8 hours to a maximum of 200 mg/day is recommended.[17]

Table I: Oral daily dosages of selected NSAIDs

NSAID	Indications	Dosage
Ibuprofen	Pain, fever, and dysmenorrhea	200–400 mg every 4–6 hours
Diclofenac	Mild to moderate pain	25–50 mg every 8 hours
	Rheumatoid arthritis	50 mg every 8–12 hours
Aspirin	Mild to moderate pain	350 mg or 650 mg every 4 hours, 500 mg every 6 hours
	Rheumatoid arthritis	500 mg every 4–6 hours, 650 mg every 4 hours, 1 000 mg every 4–6 hours, 1 950 mg twice daily
Naproxen	Pain	500 mg initially, then 250 mg every 6–8 hours. Or 500 mg every 12 hours as needed
	Rheumatoid and osteoarthritis	500–1 000 mg/day divided every 12 hours
	Dysmenorrhea	500 mg initially, then 250 mg every 6–8 hours or 500 mg every 12 hours
Indomethacin	Moderate to severe rheumatoid and osteoarthritis	Immediate-release capsule: 25 mg 2–3 times per day Extended-release capsule: 75 mg once or twice per day
	Gouty arthritis	Immediate-release capsule: 50 mg 3 times a day
	Moderate to severe ankylosing spondylitis	Immediate-release capsule: 25 mg 2–3 times per day, 50 mg per day Extended-release capsule: 75 mg once or twice per day
Paracetamol	Pain and fever	325–600 mg every 4–6 hours or 1 000 mg every 6–8 hours

Paracetamol is also administered orally and a daily dose of 325–1 000 mg every 4–8 hours to a maximum dose of 4 g/day.[16]

Drug interactions

NSAIDs have been shown to interact with several drugs, including anticoagulants, antihypertensive agents, ethanol, and antidepressant drugs. However, a key concern is the interaction between aspirin and other NSAIDs. In its low dosages, aspirin has been shown to be cardio-protective. However, concomitant use with certain NSAIDs may reduce its cardio-protective effects and increase gastrointestinal (GIT) risk.[10] In addition, it has been reported that the concurrent use of NSAIDs and warfarin or corticosteroids may also increase GIT risk. Due to the effect of NSAIDs on platelet aggregation, they may interact with anticoagulants by exacerbating their effects. In addition, NSAIDs may increase blood pressure through inhibition of certain vasodilator PGs such as PGE2 and PGI2. NSAIDs are contraindicated in patients on high-dose methotrexate, anticoagulants, or following consumption of alcohol.[18] The co-administration of NSAIDs with anticoagulants or corticosteroids may increase the risk of GIT bleeding. In addition, the co-administration with NSAIDs antihypertensive drugs may reduce the antihypertensive effects, thus increasing hypertension.

Safety and tolerability

NSAIDs have both therapeutic and adverse effects due to the inhibition of PG biosynthesis resulting in a wide range of adverse effects.[9] The most common adverse effects of NSAIDs are due to platelet inhibition, inhibition of PG formation needed for normal GIT and renal function, cardiotoxicity and hepatotoxicity, and drug-induced asthmatic responses. NSAIDs have been associated with a number of adverse effects, including GIT complications, alteration in renal function, effects on blood pressure, hepatic injury and platelet inhibition resulting in increased bleeding.[9,10] However, the most common adverse effects are GIT and cardiovascular (CV) effects. The GIT related adverse effects include ulcerations and gastric bleeding, due to the inhibition of COX-1 enzymes leading to a decreased PG synthesis that inhibits acid secretion and protects the mucosa. It has also been reported that approximately 10% of total drug-induced hepatotoxicity is NSAIDs related.[19]

Traditional non-selective NSAIDs present a greater risk of adverse effects as they inhibit both COX enzymes. Most unwanted adverse effects of NSAIDs, particularly those affecting the GIT, are due to the inhibition of COX-1 enzymes. COX-1 is thought to be involved in maintaining the integrity of the GIT mucosa and ensuring cytoprotection in the GIT.[9] It has been reported that the risk for serious GIT complications increases in patients over the age of 65 years, patients with a history of previous peptic ulcer disease, and patients taking corticosteroids, anticoagulants, and those taking aspirin.[10] NSAIDs may worsen vascular pathologies common in cardiac patients and may occasionally precipitate stroke in patients with cerebrovascular disease. It has been reported that the risk of cardiovascular events may be related to multiple mechanisms, including endothelial function and nitric oxide production, oxidative damage, blood pressure, volume retention, and renal effects.[9] In addition, it has been shown that the cardiovascular toxicity associated with NSAIDs occurs through a common mechanism involving the inhibition of COX-2 dependent PGI2.[9]

PGs are involved in controlling renin release, regulating vascular tone, and controlling tubular function. By inhibiting both COX isoforms, non-selective NSAIDs frequently lead to a transient imbalance in electrolyte and water levels resulting in renal toxicity. NSAIDs are also known to exacerbate hypertension in certain patients and to diminish the efficacy of certain antihypertensive drugs. Aspirin and non-selective NSAIDs may precipitate bronchospasm directly or via cross-allergy; thus, they may induce an acute severe asthmatic attack. In addition, NSAIDs can precipitate renal failure; thus, they should be avoided in patients with renal dysfunction.[17] It is advisable that traditional NSAIDs should not be used for more than three days for fever, and ten days for analgesia. Short term use of NSAIDs is safe and well tolerated.

NSAIDs in COVID-19 patients

It has been suggested that controlling the local and systemic inflammatory response in COVID-19 patients may be as important as antiviral therapies. As previously mentioned, NSAIDs have been used for the management of inflammation, fever, and pain for several years. However, the role of NSAIDs during viral infections is controversial, and the selective inhibition of interferon gamma production by natural killer and T-cells has been shown to be associated with a worsening clinical outcome.[20] SARS-CoV-2 causes massive cell death and cellular debris that activates inflammatory mediators, which may, in turn, trigger a macrophage-derived eicosanoid storm, and a surge of pro-inflammatory bioactive lipid mediators, such as PGs and leukotrienes that augment inflammation. It has been suggested that AA acts as endogenous antiviral compound that can contribute to the inactivation of enveloped viruses such as SARS-CoV-2.[21] A deficiency in AA may result in susceptibility to SARS-COV-2. In addition, PGE2 has been shown to play a significant role in COVID-19 pathophysiology, hyper-inflammatory and immune responses.[22]

As cytokine storm is likely to play a major role in adverse outcomes of severe COVID-19 patients, the role of anti-inflammatories such as NSAIDs may be beneficial in an effort to reduce inflammation before it overwhelms the body systems.[23] Some of the NSAIDs compounds have both antiviral and anti-inflammatory properties, making them more appropriate for treating viral respiratory infections, including COVID-19. However, there have been concerns about the appropriate role of NSAIDs in COVID-19. It has been speculated that ibuprofen may upregulate the entry point for the virus, the angiotensin-converting enzyme (ACE) 2 receptors and increase susceptibility to COVID-19 or worsen the symptoms thereof.[23] In addition, there have been reports stating that NSAIDs may exacerbate symptoms in COVID-19 patients.

Currently, there are contradicting reports of NSAIDs use by COVID-19 patients, with some recommending their use, while

others warn against their use. Similarly, NSAIDs' anti-inflammatory activity might be detrimental early in SARS-CoV-2 infection, because at this stage, inflammation is usually helpful. However, because of changes during the later stages of COVID-19, particularly if the patient undergoes cytokine storm, they may be beneficial. The contradicting reports may be due to the heterogeneous nature of COVID-19, including different strains or different cases. There seem to be COVID-19 cases where NSAIDs should not be used; however, there is no evidence that NSAIDs should be avoided in all COVID-19 patients. In addition, there is no evidence that occasional use of oral, over-the-counter NSAIDs for a few days by a person suspected or diagnosed with mild COVID-19 infection will exacerbate the infection.[23] Current guidelines recommend the use of paracetamol for temperature control in severe COVID-19 infection.[24] Paracetamol has a better safety profile over NSAIDs such as ibuprofen with respect to cardiac, gastrointestinal, and renal side effects. The most primary symptoms managed in COVID-19 infections are fever and non-productive cough; therefore, the first-line antipyretic agent is paracetamol and the antitussive of choice is guaifenesin.[25] The actual risks associated with the use of NSAIDs by COVID-19 patients is still to be determined. Currently, there is no strong scientific evidence in favour of or disputing the use of NSAIDs by COVID-19 patients. The COVID-19 infection should still be analysed, including the risks associated with NSAIDs exposure before the patients are infected.

Conclusion

Acute or chronic use of other NSAIDs has not been associated with worse COVID-19 disease outcomes. The current literature neither opposes nor support the use of NSAIDs by COVID-19 patients. More studies are required to determine the actual risk or benefit of using NSAIDs by COVID-19 patients. However, safety precautions should be considered, as there is currently not enough evidence supporting it.

Author contributions

BTF conceived, conceptualised, wrote, reviewed and edited the manuscript. NS also conceived, conceptualised, and reviewed the article.

Conflict of interest

The authors declare no financial or other competing interests that might have influenced the performance or presentation of this work.

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