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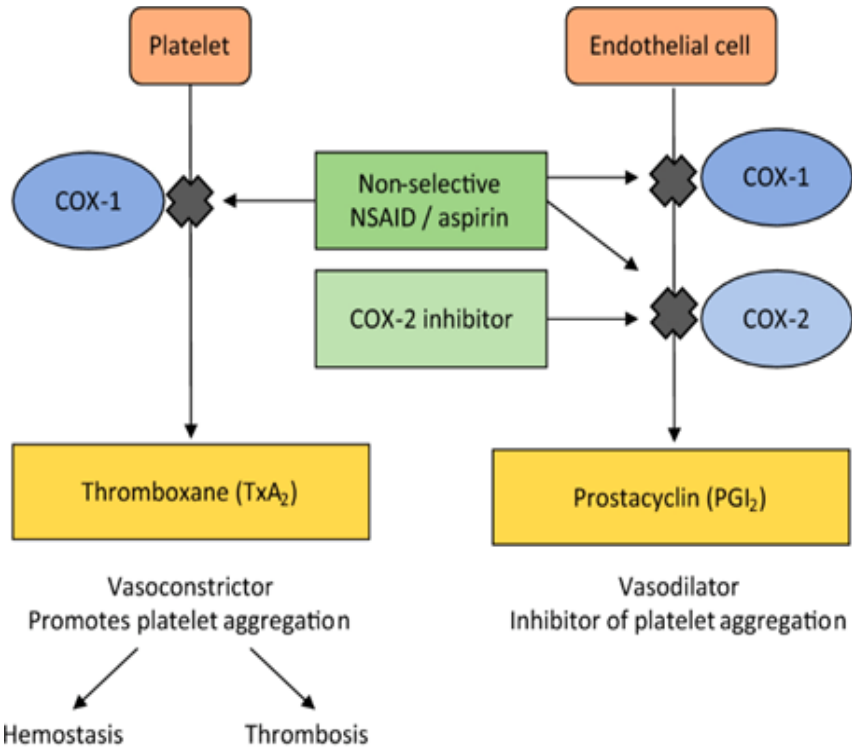
Medical Bulletin

BC Division of Blue Cross Laboratories

NSAID's (MEFENAMIC ACID) & VIRAL FEVER's

WHAT ARE NSAIDs?

NSAIDs are anti-inflammatory drugs that are used extensively for the treatment of pain and inflammation, including in patients with chronic inflammatory disorders.
NSAIDs act through the inhibition of endoperoxide synthesis enzymes, also known as cyclooxygenase (COX) enzymes that catalyze the two-step conversion of arachidonic acid into thromboxane, prostaglandins, and prostacyclin's.
Two types of COX are currently recognized: COX-1, which is constitutively expressed in the body and it is involved in homeostatic functions, and COX-2, which is expressed during an inflammatory response. COX-2 is responsible for the production of prostanoids which are involved in the processes of inflammation. Recently, there has been another COX-3 enzyme identified in the brain.
Based on their selectivity in the inhibition of COX, NSAIDs are defined nonselective, when they inhibit both COX-1 and COX-2, preferential if having more affinity for COX-2 but also inhibit COX-1 and selective if inhibiting COX-2.



HOW DO NSAIDs HELP IN THE INFLAMMATORY PROCESS?

During the inflammatory process, NSAIDs have shown to alter adherence, degranulation, phagocytosis and reactive oxygen species (ROS) production by polymorphonuclear neutrophils (PMNs). These drugs seem to reduce the recruitment of the PMNs and modify their intrinsic functions.
Furthermore, in models of acute pleural effusion, the treatment with certain NSAIDs have significantly reduced the volume of exudate and the migration of leukocytes. They have shown to inhibit TNF-α

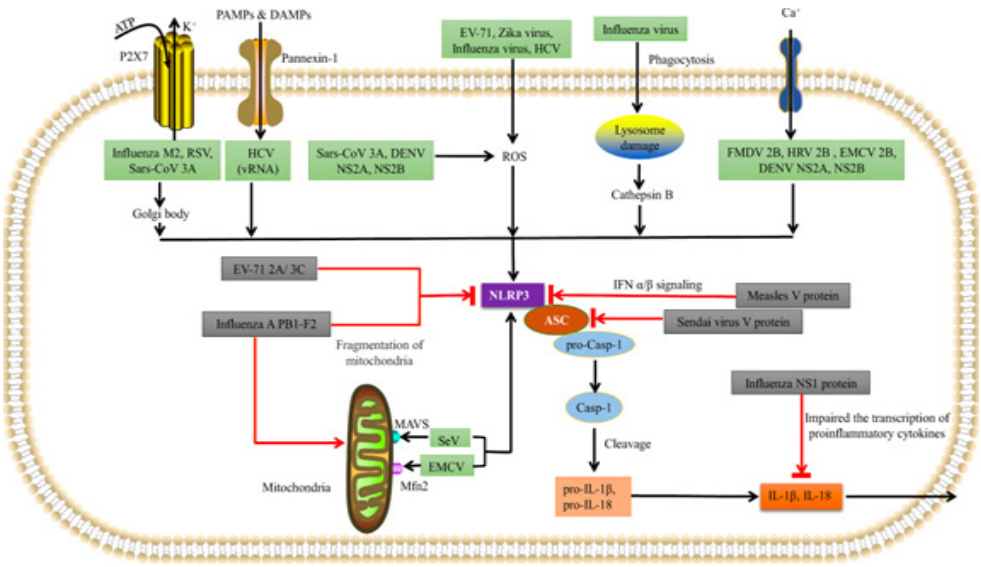
induced NFκB transcriptional activity, further contributing to reducing the local release of pro-inflammatory cytokines, including IL-8. Leukotrienes and prostaglandins stimulate the local release of lipoxins, in particular PMNs, which can interact with specific receptors on leukocytes. This leads to an inhibition of inflammation mediated by PMNs and improving the phagocytosis of PMN by macrophages.

WHAT IS THE NLRP3 INFLAMMASOME?

Many inflammatory diseases are driven by the proinflammatory cytokine interleukin-1β (IL-1β). IL-1β is produced in myeloid cells as an inactive precursor (pro-IL-1β) that requires cleavage by the protease caspase-1 for its activation and secretion.
Caspase-1 is also produced as an inactive precursor, which is activated following recruitment to a large multi-protein complex called the inflammasome.
The best characterized inflammasome-forming pattern recognition receptor, and the most commonly associated with disease is NLRP3 (NLR family, pyrin domain containing 3). In response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) NLRP3 promotes caspase-1 activation and subsequent release of IL-1β.

RNA VIRUSES THAT ACTIVATE NLRP3 INFLAMMASOME?

Various RNA viruses from various families such as Hepatitis C virus (HCV), Human immunodeficiency virus-1 (HIV1), Respiratory syncytial virus (RSV), Human rhinovirus (HRV), Zika virus (ZIKV), Influenza virus (IAV), Dengue virus (DENV), Coronavirus (SARS-CoV) can activate the NLRP3 inflammasome.
Monocytes activation and aberrant inflammasome activation have demonstrated a central role in the advancement of severe form of dengue disease. This excess inflammatory response has been demonstrated to lead to damage of the vascular barrier integrity.
Inflammasome activation plays a crucial role in controlling numerous pathogens, and thus loss of IL-1β can lead to impaired immune defense.



WHICH ARE THE NSAIDs THAT INHIBIT THE NLRP3 INFLAMMASOME?

Studies have shown that, NSAIDs like fenamates (Mefenamic acid, Flufenamic acid) selectively inhibit the NLRP3 inflammasome and IL-1β release via inhibiting the membrane volume-regulated anion (Cl−) channel (VRAC) and transient receptor protein melanostatin (TRPM2) Channels, independent of its cyclooxygenase (COX) mediated anti-inflammatory activity.

WHICH NSAIDs HAVE ANTIVIRAL PROPERTIES?

In agreement with the findings above, fenamates (Mefenamic acid) were observed to have considerable activity against viral replication.

Mefenamic acid is a serine protease inhibitor and shows significant anti-viral activity against dengue virus through its ability to inhibit viral protease activity. It has also shown to be effective in reducing viral yield in cells infected with a positive-sense RNA genome chikungunya virus.

WHAT IS THE SAFETY OF THE USE OF NSAIDs IN VIRAL FEVERS?

Concerns have been raised that NSAIDs may be associated with an increased risk of adverse effects when used in patients with acute viral respiratory infections.

This antiplatelet effect typically only poses a problem if the patient has a history of GI ulcers, diseases that impair platelet activity (hemophilia, thrombocytopenia, von Willebrand, etc.).

In case of dengue fever, the epidemiologic and cohort studies and case series describing NSAID use in dengue generally point to minimal or no significant increase in bleeding risk, except for aspirin. Meta-analyses of clinical studies across a range of clinical settings consistently conclude that NSAIDs, provides equivalent or superior analgesic and antipyretic activity compared with Paracetamol, with comparable safety.

These data suggest that the consensus guideline recommendations for Paracetamol and against NSAID use in dengue treatment should be reconsidered in light of current evidence regarding the risks and benefits of each agent.

Source: Capuano A et al. Pharmacol Res 2020; 157: 104849.; Daniels MJD et al. Nature Communications 2016; 7 (12504).; Shah A. Frontiers in Immunology 2020; 11(1021): 1-5.;Choudhry SM et al. Journal of Inflammation Research 2021: 14; 1145-1163.;Pareek RP. Int J of Science & Research 2020; 9(6): 69-73.;htt; ps://www.ncbi.nlm.nih. gov/books/NBK547742/ #!po=35. 7143.; Kellstein D & Fernandes L. Postgrad M 2019; 131(2): 109-116.;Gaurav Shrivastava et.al;Front Cell Infect Microbiol. 2020; 10: 489.

USING LOSTAT (LOSARTAN) TO TREAT HYPERTENSION & ERECTILE DYSFUNCTION

Most cases of sexual dysfunction are related to a physical cause & the common causes are diabetes, heart disease, neurological trauma or disease, & side effects of medications.

This association of ED and hypertension is explained by an age-related loss of smooth muscles from peripheral vasculature and corpora, hypertension-related endothelial dysfunction, and/or upregulation of the renin–angiotensin system (RAS).

In a study published in the American Journal of Medicine and Science, researchers found that men being treated for hypertension with the drug losartan, who also suffer from sexual dysfunction, reported improvement in at least one area of sexuality.

The 12-week study of 164 men, all with hypertension, one group with sexual dysfunction, the other group reported normal sexual functioning. Both groups took losartan in dosages of 50 to 100 mg daily for the 12 weeks. In the group of men with sexual dysfunction, 88% reported improvement in at least one area of sexual function and 73.7% reported an improved quality of life. Thus the number of men involved in the study who reported impotence dropped from 75.3 % to 11.8%.

Losartan was related with significant improvements in sexual satisfaction, frequency of sexual activity, and erectile function in patients with erectile dysfunction at baseline. On the contrary, in patients without sexual dysfunction, losartan had no effect on sexual activity.

In another study, losartan with tadalafil significantly ameliorated sexual function in patients with diabetes and erectile dysfunction compared with monotherapy with either drug. Of note, patients with mild-to-moderate erectile dysfunction responded better to losartan treatment compared with patients with severe erectile dysfunction.

The hypothesis derived from literature is that losartan may significantly prevent corporal apoptosis and oxidative stress by inhibiting the Akt/Bad/Bax/caspase-3 and Nrf2/Keap-1 signalling pathways.

Source: Clavijo et al., 2014; Jin, 2009; Kloner, 2007.;Chen, Y., Cui, S.,et al. Losartan improves erectile dysfunction in diabetic patients: a clinical trial. Int J Impot Res 24, 217–220 (2012).;Margus Y Wang e.al;Asian Journal of Andrology (2019) 21, 452–459.; Viigimaa, et.al; J Hypertens 38:1220–1234,2020.

'VITAMIN C' IN INFECTIONS

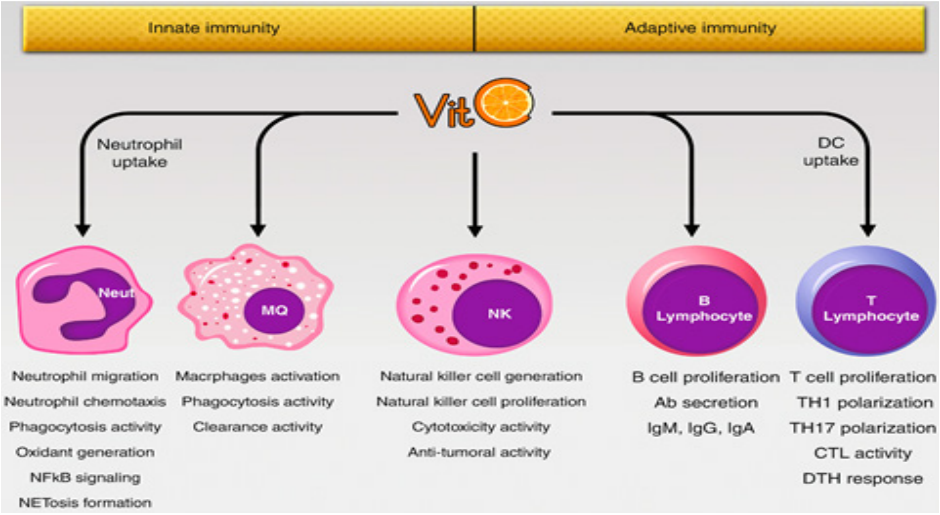
Vitamin C status can be depleted by various disease states due to inflammatory processes and enhanced oxidative stress. A number of studies of hospitalized patients have shown a high prevalence of depleted plasma vitamin C status, and its concentrations were inversely correlated with inflammatory markers.
Acute infectious diseases leading to enhanced inflammation are also associated with depleted plasma vitamin C concentrations in plasma and immune cells, as are a range of chronic infections such as HIV, H.Pylori, & tuberculosis. It should also be noted that requirements for vitamin C during infections increase with the severity of the infection, requiring significantly enhanced intakes to reach normal plasma status.
The most important roles of vitamin C is attributed to its antioxidant and anti-inflammatory property but studies have shown that vitamin C supplementation plays an important role in treatment and prevention of many infections.

VITAMIN C AND IMMUNE REGULATION

Vitamin C is known to participate in the response of the innate and adaptive immune system and the intracellular content of vitamin C in immune cells depends on the plasma availability.

- Vitamin C is involved in the migration of phagocytes (neutrophils and macrophages) toward the infection sites in response to chemo-attractants. This is particularly important since an impaired neutrophilic chemotaxis has been observed in patients with severe infection.
- In T lymphocytes, vitamin C stimulates differentiation and proliferation from precursors to mature T cells, in a dose-dependent way. The influence of vitamin C on subtypes of T cells are mainly related to the Th1/Th2 balance. Studies have shown that vitamin C can induce a shift of immune responses from Th2 to Th1.
- In B lymphocytes, vitamin C seems to affect the production of antibodies.
- Physiological levels of Vitamin C are also necessary for normal natural killer (NK) cell development and function.
- Vitamin C also regulates inflammatory response. vitamin C can reduce the production of pro-inflammatory leukocyte-derived cytokines (e.g., TNFα and IL-6), through the modulation of nuclear transcription factor kappa B (NFkB).

Apart from these functions, as an effective antioxidant, vitamin C contributes to protecting neutrophils from oxidative stress during the early stages of an immune response, when neutrophils activate phagocytosis and produce reactive oxygen species (ROS) to destroy antigens. Once the phagocytic capacity is exhausted and capacity is exhausted and neutrophils start to die, vitamin C seems to regulate the process in favour of apoptosis, through the activation of a caspase-dependent cascade, inhibiting the transition to necrosis, and resulting in a more efficient resolution of inflammation.
Similarly, to neutrophils, vitamin C also protects lymphocytes from oxidative damage and has a pivotal role in the development and function of these cells.



VITAMIN C AND VIRAL INFECTIONS

Viruses use several strategies to manipulate host cell machinery to their advantage. Among these, the imbalance of intracellular redox state caused by viruses could play an important role in modulating the activity of several signalling pathways. Oxidative imbalance caused by viral infections, ligand–receptor binding or cytokine storm could result in localised oxidation of reactive residues of redox-sensitive proteins.

Vitamin C is a potent antioxidant with anti-inflammatory and immune-supportive properties.

It plays a significant role in viral infection, including attenuation of the pro-inflammatory response, enhancement of epithelial barrier function, increased alveolar fluid clearance, & prevention of sepsis-associated coagulation abnormalities.

Vitamin C is an essential factor in the production of type I interferons during the antiviral immune response. It has also been shown to upregulate NK cell and cytotoxic T-lymphocyte activity both in vitro & in vivo. In vivo studies have shown that it plays a critical role in anti-viral immune responses against influenza virus through the increase of IFN-IL-1α/β production.

Other studies have used this vitamin as an inactivating agent both for RNA and DNA viruses, lessening viral infectivity. In addition, vitamin C can detoxify viral products that produce pain and inflammation.

VITAMIN C IN BACTERIAL INFECTIONS

Bacterial resistance to antimicrobials has become a major cause for concern. Rising antimicrobial resistance is threatening to derail much of the progress made in the field of medicine.

Vitamin C has demonstrated its antibacterial action by showing inhibitory effect on the growth of Staphylococcus aureus, Enterococcus faecalis, Helicobacter pylori, Campylobacter jejuni & Mycobacterium tuberculosis. Furthermore, in vitro studies have shown that Vitamin C can enhance the inhibitory effect of antibiotics such as levofloxacin and azithromycin.

VITAMIN C IN FUNGAL INFECTIONS

Ascorbic acid is required for the optimal activity of several important biosynthetic enzymes and is therefore essential for various metabolic pathways in the body.

Studies have shown that higher ascorbic acid concentration is inhibitory for cell proliferation and drastically reduces biomass of Candida culture and to some extent decreases virulence and pathogenicity of Candida albicans.

Vitamin C has also been shown to have an inhibitory effect on the growth of other fungi like Aspergillus.

Given the multifaceted role that Vitamin C plays against various infections, it should be strongly considered as an essential supplement.

Source: Carr AC & Rowe S. Nutrients 2020; 12(1963): 1-19.;Kim Y et al. Immune Network 2013; 13(2): 70-74.;https://www.frontiersin.org/articles/10.3389/fimmu.2020.574029/full.; Hoang BX et al. Journal of Global Antimicrobial Resistance 2020; 23: 256-262.;Verghese RJ et al. J Curr Res Sci Med 2017; 3: 88-93.;Ojha R et al. International Journal of Microbiology Research 2009; 1(1): 19-24.

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