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BC Division of Blue Cross Laboratories

VERSATILE, TIME-TESTED NSAID: MEFENAMIC ACID (MEFTAL)

Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs, inhibiting cyclooxygenase (COX) enzymes in the synthesis of prostaglandins and other inflammatory mediators, and widely used for the treatment of pain and inflammation. Mefenamic acid is a NSAID with anti-inflammatory, analgesic, and antipyretic actions. However, compared to other NSAIDs, mefenamic acid, is a preferential COX-2 inhibitor, which exhibits central and peripheral actions.

ANTI-PYRETIC

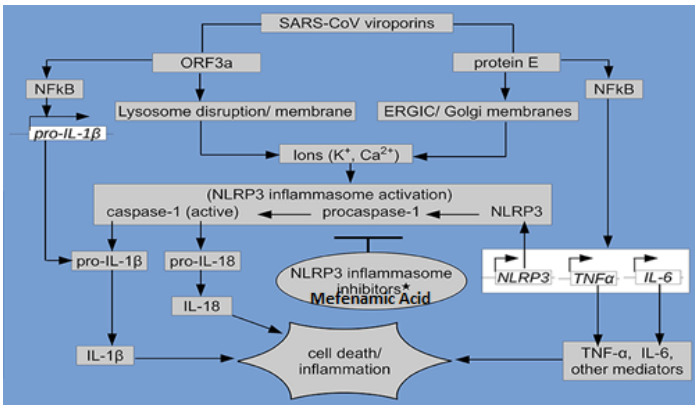
Mefenamic acid is known for its antipyretic properties and is shown to have superior efficacy than paracetamol. The anti-pyretic action of mefenamic acid is for longer duration as compared to ibuprofen and paracetamol and hence requires lesser dosing frequency.

ANTI-INFLAMMATORY & ANALGESIC

Mefenamic acid plays a versatile role in COX inhibition as it has a central as well as peripheral action. The two COX enzymes, COX-1 and COX-2, catalyse the steps for prostaglandin (PG) synthesis from arachidonic acid (AA).
Mefenamic acid is one of several NSAIDs that have shown selective inhibition of 2-arachidonylglycerol (2-AG) oxygenation by COX-2 and is deemed to be a competitive, time-dependent and reversible inhibitor for COX-1 and COX-2 enzymes.

NLRP3 INFLAMMASOME

The NLRP3 inflammasome is a critical component of the innate immune system that mediates caspase-1 activation and the secretion of pro-inflammatory cytokines IL-1ß/IL-18 in response to microbial infection and cellular damage.
However, when dysregulated, the NLRP3 inflammasome is implicated in the pathogenesis of several inflammatory disorders. Therefore, it is critical that NLRP3 inflammasome activation is precisely regulated to provide adequate immune protection without causing damage to the host tissues.



MEFENAMIC ACID AS NLRP3 INFLAMMASOME INHIBITOR

Mefenamic acid selectively inhibits the NLRP3 inflammasome and IL-1 ß release via inhibiting the membrane volume regulated anion (Cl^-) channel (VRAC), independent of its COX mediated anti-inflammatory activity.
It has been observed that there is a crucial role of NLRP3 inflammasome activation in the pathogenesis of diseases caused by SARS CoVs, and the role of inhibitors of NLRP3 inflammasome has drawn attention in the treatment of SARS CoV-2 (COVID-19), offering an opportunity for repurposing of already approved drugs.

ANTI-VIRAL

Mefenamic acid has been observed to have considerable anti-viral activity and may prevent viral replication and shows greater potential when combined with anti-viral drugs. The inhibitory effect of mefenamic acid against RNA viruses has been estimated as 90% at a concentration of 30 µM.

SERINE PROTEASE INHIBITION

Viruses like SARS CoV-2 binds to angiotensin II (ACE 2) receptor in different tissues of the body, and needs the serine protease transmembrane serine protease 2 (TMPRSS2) for cell entry.
It has been observed that mefenamic acid showed significant anti-viral activity through its ability to inhibit viral protease activity

Source:https://www.sciencedirect.com/referencework/9780080552323/xpharm-the-comprehensive-pharmacology-reference; Pareek RP. Int J of Sci & Res 2020; 9(6): 69-73.; Simila S et al. Arzneimittelforschung 1977; 27(3): 687-688.;Khubchandani RP et al. J Assoc Physicians India 1995; 43(9): 614-616.

Mefenamic acid has established itself as a valuable pharmacological agent with its versatile anti-pyretic, anti-inflammatory, analgesic and anti-viral actions.
In an era of escalating healthcare costs, a re-evaluation of existing and effective pharmacological agents is imperative. Not only do we return to using medicines that are cost effective, but we may yet realize the further potential of these agents and Mefenamic acid is a good example of this.

LOSARTAN (LOSTAT): ACTIONS BEYOND HYPERTENSION CONTROL...

The renin–angiotensin–aldosterone system (RAAS) plays an important role in the pathophysiology of hypertension and is closely related with cardiovascular and cerebrovascular events and chronic kidney diseases.

The appearance of ARBs amongst the therapeutic options in the treatment has been a new milestone in the history of hypertension treatment. According to JNC-8 guidelines, RAAS blockade by ACE inhibitors and Angiotensin Receptor Blockers (ARBs) is recommended as the new first-line therapy for the treatment of hypertension.

CARDIOVASCULAR PROTECTION

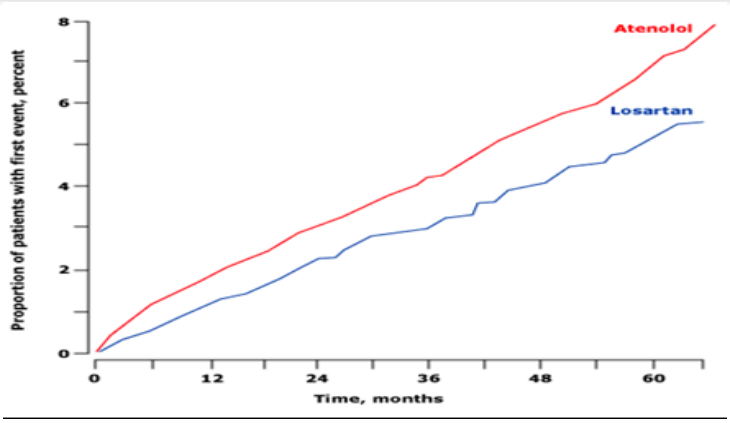
Telmisartan is the only ARB indicated for the reduction of CV morbidity, however Losartan in LIFE study has shown benefits in reducing the relative risk of MI or stroke by 13 % compared with atenolol, especially among diabetic patients, where mortality was reduced by 39%.

HEART FAILURE

Losartan has shown to be beneficial in terms of reduction of left ventricular ejection fraction as well as overall mortality related to HF.
The ELITE I & II trials have both shown that in elderly HF patients, treatment with losartan was similar to that of Captopril.

STROKE

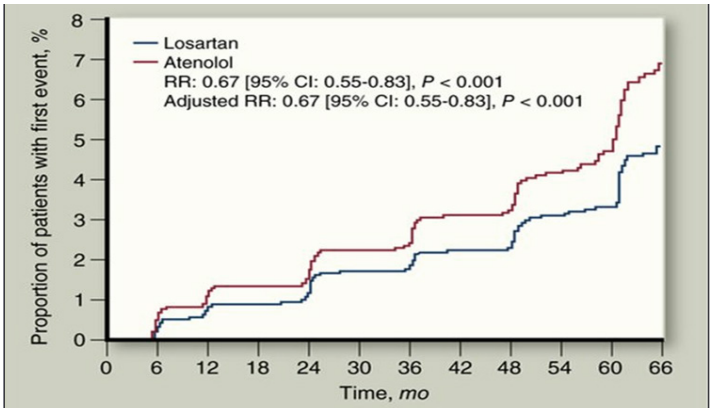
Losartan is also indicated for hypertensive patients at risk of stroke. LIFE study has shown that, losartan reduced the risk of any stroke, fatal stroke and atherothrombotic stroke significantly more than beta-blockers by 40%, 70% and 45 %, respectively.



LOSARTAN AND STROKE

ATRIAL FIBRILLATION (AF)

The use of losartan, valsartan and candesartan has been associated with a reduced incidence of new onset AF, with a relative risk reduction of 20–35 % in new-onset cases. Losartan was also found to suppress the maximum duration and the total duration of paroxysmal AF in patients with sick sinus syndrome.



LOSARTAN AND ATRIAL FIBRILLATION

PREVENTION OF DIABETES MELLITUS

The meta-analysis of LIFE, SCOPE and VALUE trials has shown losartan, candesartan and valsartan to have caused clinically significant decrease in the incidence of new onset diabetes mellitus.

RENAL END ORGAN PROTECTION

RENAAL study demonstrated losartan to reduce the risk of ESRD by 28% and decreased the level of urinary protein excretion by 35% in patients with co-existence of diabetic nephropathy.

HYPERURICEMIA

Losartan increased the excretion of uric acid and decreased the serum uric acid levels in both heathy and hypertensive patients.

ERECTILE DYSFUNCTION

ED seems to be strongly co-related with hypertension, and is also considered an early predictor of silent coronary heart disease. Treatment with losartan improved erectile function, sexual satisfaction and frequency of sexual activity in hypertensive patients. Losartan alone or in combination with tadafil significantly improved ED in diabetic patients, especially those with mild to moderate ED.

Hence, choosing the right ARB is of utmost importance in hypertensive patients, as most of the patients are predisposed to various other complications. Losartan apart from being a safe and efficacious ARB, displays a variety of other pleiotropic effects that are beneficial to the overall lifestyle associated with hypertension.

Source: Dezsi CA. Am J Cardiovasc Drugs 2016; 16: 255-266; Sivasubramaniam S & Kumarasamy B. J Clin Diagn Res 2017; 11(9): FC05-FC08.; Sakamoto T et al. Hypertension Research volume 2014; 37: 513-518.

DIABETES AND COVID-19

As the covid-19 pandemic has evolved, studies and data have revealed that not only are the covid-19 outcomes more severe in diabetics, but also have suggested that covid-19 could precipitate acute metabolic complications of diabetes such as diabetic ketoacidosis and hyperglycemia.

In a country like India, which is home to 77 million diabetics, the second largest number in the world, this becomes an additional burden with the morbidity and mortality rates of covid-19 patients. Hence, given that glycemic control is a modifiable factor and can be achieved and sustained by health-care interventions, the need arises to emphasize the importance of supporting people with diabetes in effective self-management.

HOW IS COVID-19 ASSOCIATED WITH DIABETES?

The presence of DM & the individual degree of hyperglycaemia seem to be independently associated with Covid-19 severity & increased mortality. Hypothesis being as follows-

ACE-2 RECEPTORS

Angiotensin converting enzyme-2 (ACE-2) receptor, a binding site for the SARS CoV-2, which is expressed in key metabolic organs, such as the pancreas, and in ß cells in particular. Potentially, the SARS-CoV-2 tropism for ß cells could lead to cell damage and an impairment in insulin secretion, triggering hyperglycaemia and ketoacidosis.

GLUCOSE METABOLISM

In human monocytes, elevated glucose levels directly increase SARS CoV-2 replication, & the glycolysis sustains SARS CoV-2 replication via the production of mitochondrial reactive oxygen species (ROS) & activation of hypoxia-inducible factor 1 α. Therefore, hyperglycaemia might support the viral proliferation.

INFLAMMATION AND INSULIN RESISTANCE

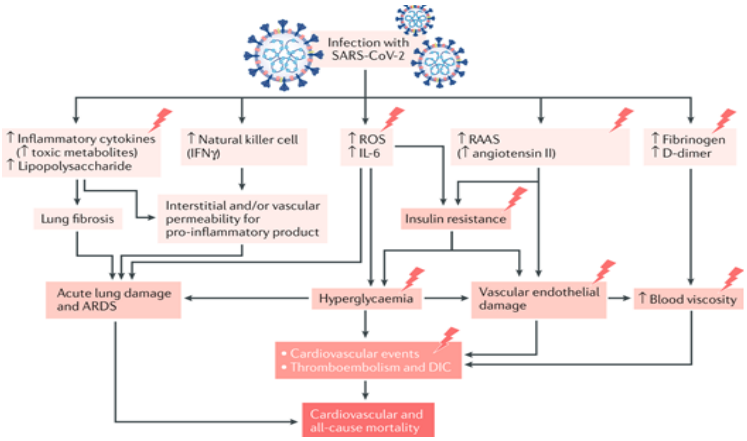
Several mechanisms have been proposed by which virally induced inflammation increases insulin resistance, one of them being that the large burden of inflammatory cells can affect the functions of skeletal muscle and the liver, the major insulin-responsive organs that are responsible for the bulk of insulin-mediated glucose uptake.
Apart from this, severe Covid-19 disease is characterized by elevated inflammatory markers like C-reactive proteins, ESR, D-dimer, ferritin and IL-6, contributing to an increased risk of microvascular and macrovascular complications originating from low grade vascular inflammation in patients with underlying diabetes mellitus, increasing the risk of mortality.

IMMUNOMODULATION

Mechanisms that link Covid-19 and both types of diabetes overlap with the pathways that regulate immune function. Hyperglycaemia can affect immune function and conversely, a dysregulated immunological status is linked to macrovascular complications of diabetes mellitus.
It has been demonstrated that acute respiratory virus infection increases IFN-Y production, and it causes muscle insulin resistance in humans, which drives compensatory hyperinsulinemia to maintain euglycemia and to boost antiviral CD8+ T cell responses and hence in patients with impaired glucose tolerance or diabetes mellitus, this compensation might fail.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

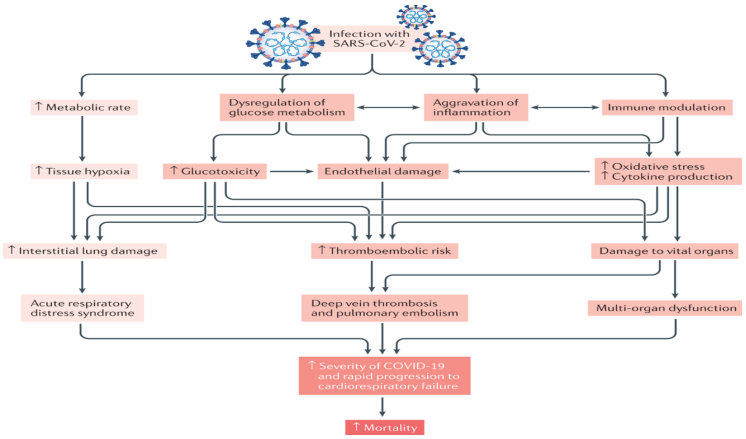
It has been shown that infection with SARS CoV-2 can cause hyperglycaemia in people without pre-existing diabetes mellitus. Based on the observation that the localization of ACE-2 expression in the endocrine pancreas, it has been suggested that coronaviruses may specifically damage islets, potentially leading to hyperglycaemia.
This suggests that the ACE-2 as a part of RAAS might be involved in the association between Covid-19 and diabetes mellitus.



POTENTIAL PATHOGENIC MECHANISMS IN PATIENTS WITH TYPE-2 DM AND COVID-19

HOW DOES DIABETES INCREASE THE SEVERITY OF COVID-19?

Glucotoxicity, endothelial damage by inflammation, oxidative stress and cytokine production contribute to an increased risk of thromboembolic complications and of damage to vital organs in patients with diabetes mellitus.
In addition, drugs often used in the clinical care of patients with COVID-19, such as systemic corticosteroids or antiviral agents, might contribute to worsening hyperglycaemia.
Therefore, it is prudent to monitor glucose levels and to treat worsening hyperglycaemia in patients with progression to severe states of Covid-19.



ACCENTUATED CLINICAL PROCESSES AFTER SARS CoV-2 INFECTION IN DIABETIC PATIENTS

Coronavirus infections are proven to have a huge effect in the management of diabetes mellitus because as it aggravates inflammation as well as alter immune system responses, leading to difficulties in glycemic control. SARS CoV-2 infection also increases the risk of thromboembolism and is more likely to induce cardiorespiratory failure in patients with diabetes mellitus than in patients without diabetes mellitus. All of these mechanisms are now believed to contribute to the poor prognosis of patients with diabetes and Covid-19.

Source:https://www.thelancet.com/journals/landia/article/PIIS2213-8587(20)30315-6/fulltext.;https://www.thehindu.com/sci-tech/health/india-has-second-largest-number-of-people-withdiabetes/article29975027.ece#:~:-text=India%20is%20ho me%20to%2077%20million%20diabetics%2C%20second%20highest%20in%20the%20world,-Ramya%20Kannan.; Lim S et al. Nature Reviews Endocrinology volume 2021;17: 11-30.

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