QUARTER 3, 2021 | VOLUME 9 | NUMBER 6

EXCEL Medical Bulletin

EXCEL Division of Blue Cross Laboratories

Combining NSAIDs(MEFTAGESIC-P: Mefenamic acid + Paracetamol)... An Effective Approach to Fever Management

Fever is one of the most important and common presenting symptoms in clinics, out patient departments and emergency. Fever may be defined as a complex physiologic response to a disease, mediated by pyrogenic cytokines and characterized by a rise in core temperature, generation of acute phase reactants and activation of immune systems.

Regulation of body temperature requires a delicate balance between production & loss of heat. Hypothalamus regulates the set-point at which the body temperature is maintained. In fever this hypothalamus thermostat set point is elevated & body temperature increases over normal values.

In most clinical situations, fever results from the presence of the substances called pyrogens. Various infections, toxins and other mediators induce production of pyrogens by host inflammatory cells such as macrophages, endothelial cells and lymphocytes. The endogenous pyrogens produced locally or systemically gain entrance in the circulation and produce fever. The major fever causing cytokines are various Interleukins (ILs) like IL-Iβ, 1L-6, TNF-α (Tumor necrosis factor) and INF-α (interferon).

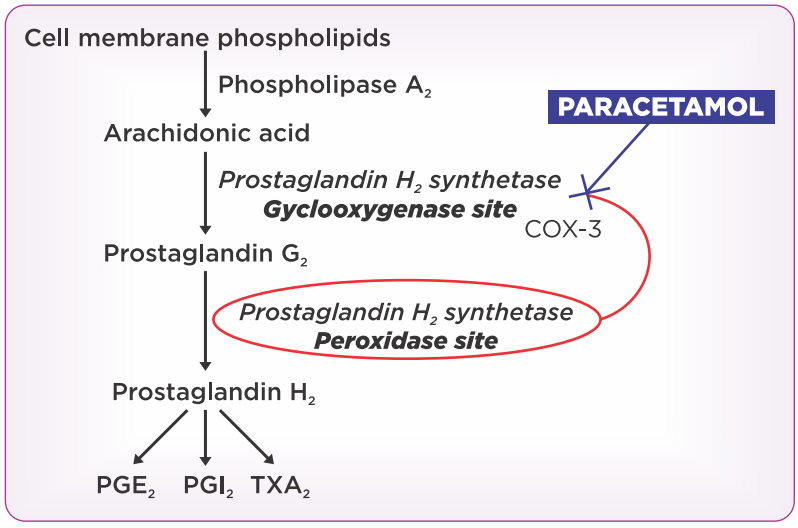
These pyrogenic cytokines directly stimulate the hypothalamus to produce PGE2 (prostaglandin E2) which then resets the temperature regulatory set point. IL-1β is an important pyrogenic cytokine that on reaching the hypothalamus induces fever.

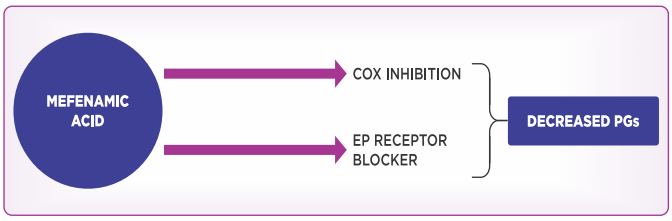
Anti-pyresis one of the most usual therapeutic interventions undertaken. The most commonly used antipyretics are Nonsteroidal Anti-Inflammatory Drugs(NSAIDS), which also have a considerable analgesic effect which promotes a general feeling of well-being.

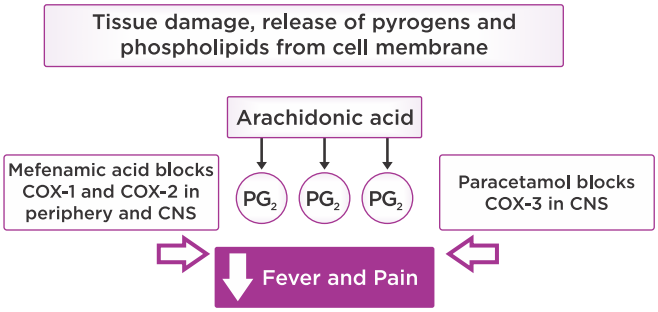
NSAIDs inhibit the enzymes cyclooxygenases(COX), mainly COX-1 and COX-2 which catalyzes the conversion of arachidonic acid to prostaglandin E2. This reduction of prostaglandin E2 in the brain is believed to lower the hypothalamic set point.

A variety of pharmacological agents are available for anti-pyresis. Among these Paracetamol, Ibuprofen, and Mefenamic acid are the most commonly used agents.

Paracetamol's antipyretic effect is thought to be caused by its ability to diminish the synthesis of prostaglandin in the brain through inhibition of lesser known Cox-3 enzyme. However, paracetamol doesn't possess peripheral PG inhibitory action.







Whereas, Mefenamic acid, a NSAID, is a Preferential COX inhibitor with both central and peripheral actions. It also blocks the EP receptors thereby blocking the action of pre-formed Pgs.

Combination of Paracetamol and Mefenamic acid provides comprehensive inhibition of the COX enzymes in the brain as well as in the periphery, thus providing better antipyretic, analgesic and anti-inflammatory effects.

In-terms of the pharmacological properties, Paracetamol is readily absorbed and rapidly distributed to the tissues in the body, providing a faster onset of action whereas, Mefenamic acid takes one hour to act but its effect last long. Hence, combining them gives faster onset as well as longer duration of action for fever control.

Studies conducted on pediatric patients having febrile illness have shown that the combination of Paracetamol with Mefenamic acid had better anti-pyresis at one hour as compared to paracetamol alone.

Literature indicate there are cases of fever that do not respond to Paracetamol and this trend is increasing. This is not the case with Mefenamic acid and thus combination of Mefenamic Acid and Paracetamol is a good option for effective antipyresis.

Source:Rao MS & Sailaja G. IOSR Journal of Dental and Medical Sciences 2015; 14(3): 05-09; Reddy GT et al. Int J of Scientific Study 2020; 8(6): 58-62.

K-Met(Metformin)... Beyond Glycemic Control

Metformin is a widely used biguanide drug that has been used over the years to treat type 2 diabetes at the early stages because of its outstanding ability to decrease plasma glucose levels as well as an excellent safety profile.

Over time, different uses of Metformin beyond its glycemic control have been discovered. Studies showed that Metformin exerts a strong effect on numerous cancers, cardiovascular disease (CVD), liver diseases, obesity, neurodegenerative diseases, & renal diseases. Solely or in combinations with other drugs has shown it to be effective to treat different diseases.

WHAT IS THE MAIN ACTION OF METFORMIN IN DIABETES?

Metformin exerts its anti-hyperglycaemic effects mostly by suppressing hepatic glucose production through (adenosine 5'- monophosphate-activated protein kinase) AMPK-dependent as well as independent pathways.

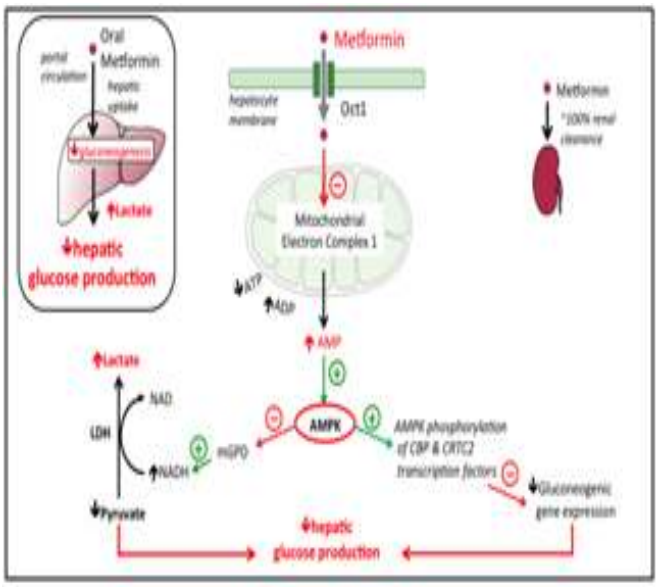
Metformin inhibits mitochondrial complex I, which leads to AMPK activation. Mitochondrial complex I is vital to electron transport. As a result, the production of ATP (adenosine triphosphate) decreases & the intracellular concentration of ADP (adenosine diphosphate) increases. Consequently, the cellular levels of AMP (adenosine monophosphate) increases, finally activating AMPK.

AMPK is a key regulator of numerous metabolic pathways, including glucose metabolism, lipid metabolism, and energy homeostasis.Also, activation of AMPK leads to the inhibition of mTORC1 (mammalian target of rapamycin complex I), which also results in the suppression of gluconeogenesis.

On the other hand, Metformin inhibits hepatic glucose production in an AMPK-independent manner. Metformin attenuates the ability of glucagon or inhibits mitochondrial GPD (glycerol-3-phosphate dehydrogenase), subsequently leading to an impairment of lactate utilization for gluconeogenesis.
A study has also demonstrated that Metformin directly targets FBP1 (fructose-1,6-bisphosphatase-1), the rate controlling enzyme in gluconeogenesis, inhibiting hepatic glucose production.

Other studies have suggested that Metformin could also enhance GLUT1 (glucose transporter 1) mediated glucose transport into hepatocytes through activating IRS2 (insulin receptor substrate two), decreasing plasma glucose levels.

Apart from its role in diabetes, Metformin also has shown a significant role in many other diseases due to its versatile actions.



METFORMIN IN CANCER

Metformin's anti-cancer properties depend on its direct and indirect regulation of the cells' metabolism. The direct effects are mediated by AMPK-dependent and independent pathways.

- Metformin activates AMPK, which leads to the inhibition of mTOR signalling, and as a result, protein synthesis is disturbed, and cell growth and proliferation is suppressed.
- Metformin also inhibits mTORC1, directly a key regulator of cell growth that can integrate intracellular and extracellular stimuli, in an AMPK-independent manner.
- Additionally, Metformin suppresses mitochondrial complex I, thereby preventing the generation of reactive oxygen species (ROS) and further decreasing DNA damage, suppressing cancer development.

METFORMIN AND OBESITY

Obesity is a multi-factor chronic disease accompanied with other related metabolic syndromes, such as diabetes, fatty liver diseases, and CVDs. Obesity is caused by an imbalance between energy intake and expenditure. Accumulating evidence have suggested that metformin may be a potential therapy for obesity and its related metabolic dysfunctions.
In non-diabetic individuals, Metformin was shown to exert weak but beneficial effects on weight loss. It has been observed that Metformin significantly prevented high-fat diet induced obesity and the associated inflammatory response through increasing the expression of FGF21 (fibroblast growth factor 21), a key metabolic hormone that improves lipolysis in white adipose tissue to prevent fat accumulation.

It was shown that Metformin exerts its anti-obesity effects through increasing mitochondrial biogenesis, decreasing fatty acid uptake, and stimulating thermogenesis.

METFORMIN AND LIVER DISEASE

The liver, which plays a critical role in the physiology of the whole body, especially glucose homeostasis and lipid metabolism, is the main target organ of Metformin.

- Metformin was also found to reduce the incidence of fatty liver diseases and to cause a histological response.
- The main contributor to non-alcoholic fatty liver disease (NAFLD) is the disorder of hepatic lipogenesis, a process relevant to several transcription factors, which affects the expression of key enzymes of lipogenesis. Insulin resistance is also able to induce NAFLD by the famous “two-hit” theory. Metformin treatment induces AMPK activation, leading to a reduction in ACC (acetyl-CoA carboxylase) or SREBP1c (Sterol regulatory element-binding protein 1) inhibition, which in turn reduces fatty acid oxidation and suppresses fatty acid synthesis.
- Apart from this, Metformin modulates the synthesis of adipokines like TNF-alpha and IL-6, which increase fatty acid oxidation and decrease lipogenesis.

METFORMIN IN CARDIOVASCULAR DISEASE

Hyperglycaemia induces oxidative stress, resulting in lipoprotein dysfunction and endothelial dysfunction, increasing the risk of CVD.

- Metformin, through activating AMPK, inhibits modification of apolipoprotein residues, consequently ameliorating high-density lipoprotein (HDL) dysfunction and reducing low-density lipoprotein (LDL) modifications. Reductions in HDL dysfunction improves cholesterol transport and diminishes the cardiovascular risk.
- Moreover, Metformin improves endothelial oxidative stress levels and attenuates hyperglycaemia-induced inflammation, decreasing the occurrence of CVD.
- It has been shown that Metformin improves the myocardial energy status through ameliorating cellular lipid and glucose metabolism via AMPK.

METFORMIN AND RENAL DISEASE

- Diabetes is considered as an important cause of renal diseases, and metformin is an interesting candidate to treat renal diseases.
- Studies showed that daily oral administration of Metformin could ameliorate kidney fibrosis and normalize kidney structure and function. These effects may be mediated by the AMPK signalling pathway, which can regulate cell growth and energy utilization.
- Clinical trials suggested that continuous Metformin administration improved renal function and survival in patients with Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD).

METFORMIN AND AGEING

The declining ability to regenerate damaged tissue and the deterioration in homeostatic processes are considered as biological features of aging which increases the probability of many health outcomes.

Aging is a result of DNA damage, which can be induced by ROS, alkylation, hydrolysis, chemicals, and ultraviolet and other radiation. Genetic and environmental factors involved in the regulation of autophagy are also critical factors in the aging process.

The mechanisms by which Metformin affects the aging process are partly dependent on the regulation of glucose metabolism.

- By inhibiting mitochondrial complex-I, Metformin reduces endogenous production of ROS and subsequently decreases DNA damage.
- By activating AMPK, Metformin is able to inhibit NF-KB signalling and attenuate cell inflammation. Metformin also leads to decreased insulin levels, and suppresses IGF-1 (Insulin like growth factor 1) signalling and mTOR signalling, which together results in suppression of inflammation and autophagy that is beneficial to the aging process.
- Besides, Metformin was shown to have a function in the regulation of the microbiome, which may be another way to affect aging.
- In addition, Metformin reduces neuronal injury and improves oxygen/glucose deprivation, thereby improving neuronal survival and neuroprotective functions.

Metformin has shown to have beneficial effects on liver diseases, obesity, cardiovascular diseases, age-related diseases, and renal diseases, thus finally decreasing death risk. These actions of Metformin are attributed to AMPK activation or mitochondrial complex inhibition, subsequently affecting cell metabolism.

This knowledge may provide new potential therapeutic targets & given its known safety & long-term use, Metformin is becoming a promising treatment option for many diseases.

Source:Ziquan LV &Guo Y. Frontiers Endocrinol 2020; 11(191): 1-10.

Unique features of R-PPI (RABEPRAZOLE)

Proton pump inhibitors (PPIs) are the most effective drugs to control GERD symptoms. Rabeprazole is a PPI that effectively provides symptom relief & healing, and prevents relapse, in patients with erosive GERD.Rabeprazole achieves high healing rates and effective symptom relief in patients with GERD, duodenal ulcers, and gastric ulcers, and it has demonstrated a consistently favorable tolerability profile.

Pharmacodynamic data show rabeprazole can achieve optimal acid suppression since the first administration and can maintain this advantage in the following days of therapy.In particular, this drug has a very fast onset of action, due to a short activation time and a very high pKa (the pH at which a drug becomes 50% protonated).

Several studies inferred that rabeprazole was a better choice in mild-to-moderate erosive GERD and several following mechanisms may explain its superior efficacy:-

- Rates of acid inhibition are known to correlate with the acid stability of PPIs. Rabeprazole, which has the highest pKa of all PPIs and is therefore least stable at neutral pH, is more rapidly converted to inhibit the proton pump.
- Rabeprazole achieves maximal inhibition within 8 mins of drug exposure.
- Rabeprazole accumulates to higher levels which contributes to faster onset of inhibition of acid secretion, especially in older cells which weakly secrete acid (pH 3). In older parietal cells, rabeprazole can be as much as 10 times more potent than other PPIs.
- Rabeprazole may have more prolonged and potent acid inhibitory effects due to continued binding to proton pump transmembrane domains even after achieving 100% inhibition of the ATPase activity.
- However, in less acidic environments, rabeprazole, given its rapid activation over a wide pH range, actually targets a greater population of parietal cells to give a more rapid and pronounced degree of acid inhibition.
- In addition, rabeprazole has an advantage not shared by other PPIs. Its metabolism is largely non-enzymatic and therefore less dependent on CYP2C19, giving a greater consistency of pharmacokinetics across all patients, regardless of the CYP2C19 genotype.
- Recent studies have also indicated that rabeprazole on-demand is cost effective in preventing non-erosive reflux disease (NERD) symptom relapse.

Source:Maiti R et al. J PharmacolPharmacother 2011; 2(3): 150-157; Indra A et al. National Journal of Basic Medical Sciences 2020: 10(4): 147-157; Pace F et al. TherClin Risk Manag 2007; 3(3): 363-379.

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