QUARTER 2, 2023 | VOLUME 11 | NUMBER 3

Medical Bulletin

BC Division of Blue Cross Laboratories Pvt Ltd.

MEFTAL SPAS NEO DROPS (SIMETHICONE) FOR RELIEVING COLICKY PAIN AND FLATULENCE IN INFANTS

"Colicky pain is a condition in which there is sudden involuntary contraction of a muscle or a group of muscles associated with sudden pain"

Colic is a common phenomenon in infants

Characterized by excessive and paroxysmal crying

Affects up to **40%** of infants worldwide

Associated with....

- Flatulence
- Gastrointestinal spasm
- Abdominal pain

Management:

- Parental behavioral interventions
- Dietary/Nutritional modification
- Pharmacological intervention

Simethicone	Safe anti-flatulent agent for relieving colicky pain & flatulence/abdominal pain in infants
Dosage	Infants (0-12 months): 20 mg/dose 3 to 4 times daily. Maximum: 240 mg/day

AS PER

- Centers for Disease Control & Prevention (CDC)
- US Food & Drug Administration (FDA)
- Institute for Safe Medication Practices
- American Academy of Pediatrics (AAP)
- American Academy of Family Physicians (AAFP)

BENEFITS OF DOSING IN MILLILITER (mL)

- Improves dose clarity
- Improves dose consistency
- Reduces rate of administration errors
- Promotes safe use of pediatric liquid medications

Source: JB Banks, et al. https://www.ncbi.nlm.nih.gov/;Buckle J. Clinical Aromatherapy (3 rd Edition).2015; Yin HS, et al. Pediatrics. 2014; 134(2): 354-361.

Colicky Pain in Infants

℞ MEFTAL-SPAS® NEO

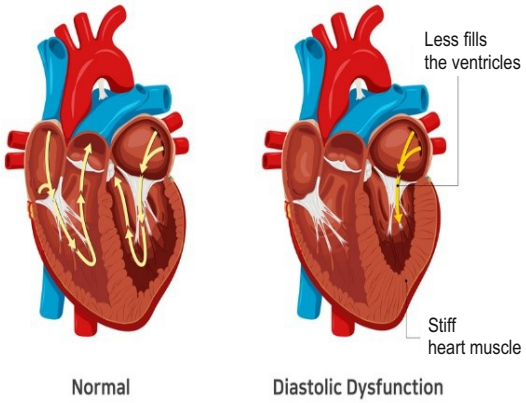
Simethicone 40 mg. / 1 ml Drops

With Dill Oil & Fennel Oil

K-PIO (PIOGLITAZONE) IMPROVES LEFT VENTRICULAR DIASTOLIC DYSFUNCTION (LVDD) IN TYPE 2 DIABETICS

Diastolic Dysfunction is frequent in patients with type 2 diabetes (T2DM) and is associated with poor prognosis. The prevalence of diastolic dysfunction in patients with T2DM is up to 75% and correlates with the degree of glucose dysregulation.

LEFT VENTRICULAR DIASTOLIC DYSFUNCTION



Left ventricular diastolic dysfunction (LVDD) is considered as the first manifestation of cardiac remodeling in diabetes mellitus and represents the earliest, pre-clinical manifestation of diabetic cardiomyopathy preceding systolic dysfunction and evolving to symptomatic heart failure.

It is defined as the inability of the ventricle to a normal end-diastolic volume, both during exercise as well as at rest while the left atrial pressure does not exceed 12 mm Hg. LVDD is associated with adverse cardiovascular outcomes in T2DM patients and delaying or preventing LVDD could reduce hospitalization and mortality among T2DM patients.

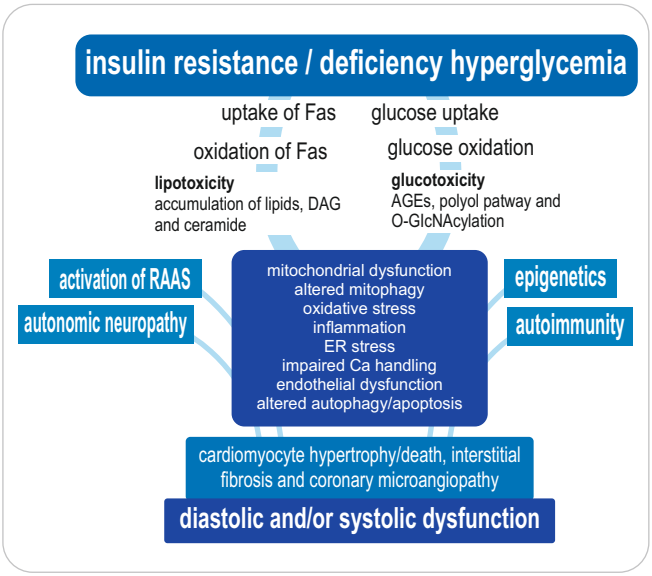
Pathophysiology

The pathophysiology of diastolic dysfunction involves delayed relaxation, impaired LV filling and/or increased stiffness. These conditions result in impaired diastolic relaxation ability and decrease myocardial compliance.

Structural myocardial changes are detected in the early stages of the disease even before its first clinical manifestation. The first visible structural change in the cardiomyocytes is slight myocardial hypertrophy accompanied by perivascular and interstitial fibrosis as well as collagen deposition. In addition to macroscopic remodeling, cardiomyocytes also undergo microscopic and ultrastructural changes.

Pathways involved in metabolic and structural changes in the early cardiomyocyte damage:-

- **Metabolic disturbances:** Decreased glucose oxidation, increased free fatty acid.
- **Impaired cellular function:** Inadequate calcium signaling, augmented oxidative stress and mitochondrial dysfunction.
- **Structural alterations:** Accumulation of AGE products (advanced glycation end-products), cardiomyocyte hypertrophy.
- **Activation of renin-angiotensin-aldosterone system (RAAS):** Fibrosis and cardiomyocyte stiffness.
- **Cardiac autonomic neuropathy:** These are triggered by hyperglycemic and lipotoxic anomalies related to insulin resistance.



Myocardial insulin resistance is thought to be a risk factor for cardiac dysfunction and coronary atherosclerosis. The diabetic heart has been postulated to lose its metabolic flexibility because of myocardial insulin resistance which is associated with myocardial lipid accumulation, inflammation, increased collagen formation, myocardial stiffness and a non-compliant left ventricle.

Extracellular matrix (ECM) and Collagen

The extracellular matrix (ECM) is composed of collagen, elastic fibers, glycosaminoglycans and glycoproteins- all derived from fibroblasts which are necessary to maintain the normal structure and function of the heart . In pathological conditions, because of the maladjustments of the matrix metalloproteinases (MMPs) and excessive secretion of some regulatory cytokines like transforming growth factor-β (TGF-β) the dynamic balance is broken resulting in cardiac fibrosis. The myocardial collagen network mainly consists of type I and type III collagen which have different physical properties & help maintain the functional integrity of the heart. Type I collagen provides rigidity whereas type III collagen contributes to elasticity. The alterations in the collagen framework play an important role in ventricular dysfunction of ischemic or non-ischemic origin.

It has been postulated that the growth of type I collagen is limited by type III collagen and therefore, a change in the ratio that results in the formation of less type III and more type I ,resulting in an increase in thicker fibrils. This shift towards thicker fibrils in hearts with dilated cardiomyopathy may be caused by an imbalance in either formation or degradation between two types of collagen.

PERIXISOME PROLIFERATOR ACTIVATED RECEPTOR GAMMA (PPAR-γ)

PPARγ presents many pleiotropic effects and Pioglitazone has demonstrated to decrease myocardial fibrosis and improve cardiac dysfunction. PPARγ reduces myocardial fibrosis by inhibition of the proliferation and migration of vascular smooth muscle cells and the expression of the profibrotic agent, TGF-β and negatively influences cardiac hypertrophy, improves LVDD and decreases collagen accumulation in the cardiomyocytes.

PPARγ activation modulate the expression of the ECM proteins by targeting the transforming growth factor β-1(TGF-β1) and mitogen-activated protein kinase (MAPK) pathways.

Thiazolidinediones exhibit PPARγ agonist action & inhibits the cardiomyocyte growth and inhibits cardiac hypertrophy via the PPARγ dependent pathway. However, this is not necessarily a class effect and the beneficial effects on cardiac hypertrophy are restricted to Pioglitazone whereas Rosiglitazone may on the contrary cause cardiac hypertrophy though PPARγ independent pathways.

CLINICAL EVIDENCES SUPPORTING PIOGLITAZONE

Pioglitazone modulates the expression of ECM proteins by targeting the TGF-β and MAPK pathways.

Pioglitazone, apart from its actions dependent on PPARγ inhibiting cardiac hypertrophy is known to block the P38MAPK signaling pathway through the PPARγ independent pathway by blocking the phosphorylation of P38MAPK and prevents cardiac hypertrophy and remodeling. Additionally, pioglitazone has shown to significantly decrease the expression of mTOR which contributes to the development of cardiomyocyte hypertrophy.

On the contrary, Rosiglitazone, independent of its PPARγ action, increases the phosphorylation of P38MAPK which is sufficient to cause cardiomyocyte apoptosis and cardiac hypertrophy.

Various studies support this hypothesis and the benefits of Pioglitazone in cardiac hypertrophy outweigh the benefits of Rosiglitazone.

Recently, in a meta-analysis with seven studies on 233 patients, apart from an improvement in the HbA1c levels, a significant improvement in the LVDD was observed with the use of Pioglitazone in T2DM patients of age < 55 years at doses 15-45 mg for a treatment duration of 16-24 weeks.

Convincing data support the anti-fibrotic effect of Pioglitazone in cardiac remodelling in several studies documenting a consistent reduction in cardiac fibrosis by reducing the deposition of ECM, synthesis of collagen I and III, tissue inhibitor of metalloproteinase (TIMP-1) and MMP-2, all involved in the cardiac remodelling and contributing to cardiac hypertrophy.

Another 6 month study on 12 patients determining the effect of Pioglitazone on insulin sensitivity in the cardiac tissue and LV diastolic function, it was observed that treatment with Pioglitazone not only increased the myocardial glucose uptake, but also improved the parameters of diastolic function with an increase in trans-mitral early diastolic relaxation/arterial contraction ratio and the peak ventricular filling rate. There was also an increase in stroke volume and ejection fraction with improvement in the

parameters of systolic function. On the contrary, Rosiglitazone was shown to have negative effects on cardiac function and was associated with an increased incidence of cardiac hypertrophy.

The DREAM trial, a large placebo-controlled trial on the use of Rosiglitazone in patients with impaired glucose tolerance and impaired fasting glucose but no underlying cardiovascular disease, showed an increase in abnormalities in LV diastolic function and advanced LVDD.

Similarly, a multi-centre, open-label RECORD study and a meta-analysis of randomized trails showed that the use of Rosiglitazone was associated with a higher risk of heart failure and heart failure events.

To conclude, Pioglitazone based on its PPARγ independent action plays a beneficial role in cardiac remodelling and improves LVDD, especially in patients with T2DM making it a suitable treatment option in young T2DM patients in order to prevent related cardiac events.

Source: Han Song MM et al. Medicine (Baltimore) 2023; 102(1): e32613;. Hu A & Wu X. Indian J of pharmaceutical Sciences 2022; 84(5): 1297-1302; Hu A & Wu X. Indian J of pharmaceutical Sciences 2022; 84(5): 1297-1302.Kumarathurai P et al. Cardiovascular Diabetology 2021; 20(12); Bachewar PA et al. Medpulse Int. Journ.of Med. 2021; 18(3): 68-71.; Nesti L et al. Cardiovascular Diabetol 2021; 20: 109.;Grigorescu ED et al. Diagnostics 2019; 9(3): 121.;

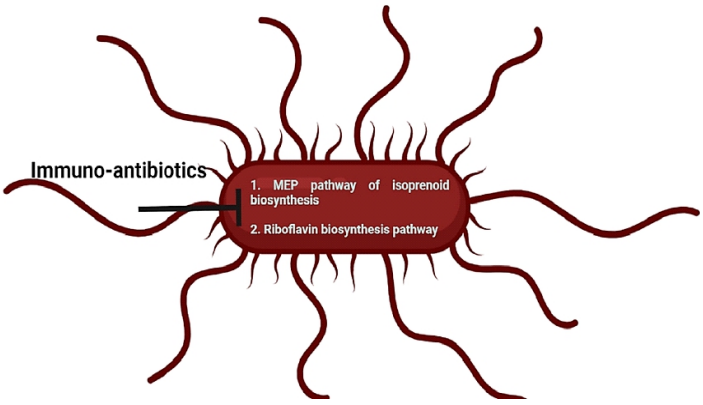
COMBATING ANTIBIOTIC RESISTANCE USING DUAL ACTING IMMUNE ANTIBIOTICS (DAIAs)

It is estimated by 2050 Antimicrobial resistance (AMR) could claim 10 million lives each year & WHO has declared it as one of the top global public health threats. The list of bacteria that are becoming resistant with all available antibiotic options is increasing whereas the number of new drugs being investigated are unable to match with. Thus, creative strategies to combat this issue needs to be developed.

One of the recently researched interventions is a double-pronged approach to develop new molecules that can tackle difficult-to-treat infections while enhancing the natural host immune response.

The use of Dual acting immune-antibiotics (DAIAs) acting immune-antibiotics provides a dual approach that combines the killing capabilities of antibiotics with the harnessing of the inherent immune system, simultaneously attacking the bacteria on two different fronts, generating synergy and making resistance development more difficult.

Metabolic pathway that is essential for most bacteria but absent in humans is an ideal target. The Methyl-D-erythritol phosphate (MEP) pathway (isoprenoid biosynthesis) or the non-mevalonate pathway and the riboflavin biosynthesis pathway in the bacteria are required for the cell survival for most pathogenic bacteria. The enzyme, isoprenoid H synthetase (IspH) is an essential enzyme and has been studied in vitro as a target to block this pathway and affect the survival of the pathogen. The IspH inhibitors when tested in vitro on antibiotic resistant bacteria have been observed to stimulate the immune system and help in better bacterial clearance and specificity.



Another pathway for the use of immune-antibiotics is the riboflavin biosynthesis pathway. It is present in almost all bacteria and fungi, but it is absent in humans and other animals, which makes it an attractive drug target. Immuno-antibiotics target the final two steps of the riboflavin synthesis catalyzed by lumazine synthase (RibE or RibH) and riboflavin synthase (RibC), thus affecting the survival of the pathogenic bacteria.

Antibiotic resistance remains an internationally worrisome problem that requires urgent intervention. The approaches that block key metabolic pathways is a viable alternative to the “one compound, one target” model that has dominated antibiotic drug development. The development of agents with the dual activity of inhibiting bacteria while also enhancing the immune system appears to be a promising strategy and can address the need of the hour.

Source: Nwobodo DC et al. J of Clin Lab Analysis 2022; 36(9): e24655; Jamod H et al. ASSAY & Drug Development Technologies 2022; 20(5): 225-236; https://www.sciencedaily.com/releases/2020/12/201223125759.htm

Dr. Prabhu Kasture (MD, DPH)
Dy. Director Medical Services & Pharmacovigilance

PHONE NO.: 022-666638043
EMAIL: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt. Ltd. (Peninsula Corporate Park, Peninsula Chambers, Ganpatro Kadam Marg, Lower Parel, Mumbai-400013