

Meldonium: drug which brought disrepute to sport**Bikash Ranjan Meher^{1*}, Smita Das², Rashmi Ranjan Mohanty³**

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ABSTRACT

World of sports have been rocked by doping scandals every now and then and World Anti-Doping Agency(WADA) has banned several offending drugs at different times to counter this menace. Meldonium is the recent addition to the long list of drugs banned by WADA to prevent its misuse among the athletes. Meldonium is a carnitine synthesis inhibitor and has been approved by some European countries for the management of cardiac diseases like angina pectoris and congestive cardiac failure. Apart from these, it has numerous other indications like bronchial asthma, bronchitis and retinopathies. It had also been used by athletes across the world because of its presumptive role in increasing the performance.

Keywords: Doping, L-Carnitine, Meldonium

INTRODUCTION

Sport has always been marred by doping scandals and controversies. But it reached mammoth proportion, when part of Russian contingent was banned from Rio Olympics. In the beginning of this year tennis fans across the world were stunned by the shocking revelation of doping scandal involving a numero uno Russian tennis player, it was found that she was taking Mildronate for quite a long time, subsequently she was handed over a temporary ban by world tennis federation. Because of this

and some other similar events in other disciplines of sport involving it, meldonium grabbed the eye ball across the world and adorned prominent pages in various newspapers. In view of these, world anti-doping agency (WADA) added this drug in its prohibited list, effective from first January 2016, although it was an old drug.¹

So, what exactly is Mildronate? This question is lurking in the mind of people in general and sport enthusiasts in particular across the world.

Mildronate is the brand name of meldonium. It was first manufactured by Baltic (Latvian) pharmaceutical company Grindeks and introduced as a growth promoting agent in animals.² It was found to increase sperm motility, serum testosterone concentration and sexual performance in boar.³ Later different clinical studies established it as an agent having anti-ischemic and cardio protective effect.^{4,5} A large number studies had been carried out to explore its pharmacological effects and therapeutic benefits.⁵ Most of its therapeutic effects are linked to its role in carnitine metabolism. This drug is not yet approved for use in USA or Western European nations, but available as both OTC (over the counter) and prescription drug in Eastern Europe.

STRUCTURE OF MELDONIUM

Chemically, meldonium is 3-(2, 2, 2-trimethylhydrazinium) propionate dihydrate. Its chemical structure resembles that of L-Carnitine and γ butyrobetaine (Figure 1 and Figure 2).⁶

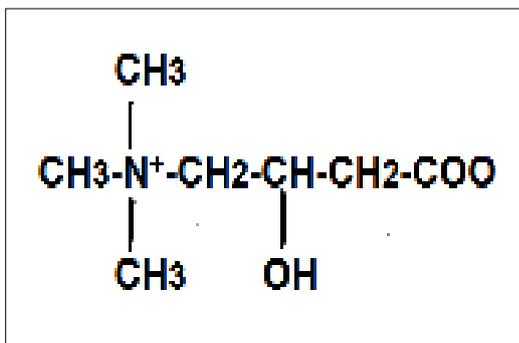


Figure 1: Chemical structure of L-Carnitine.

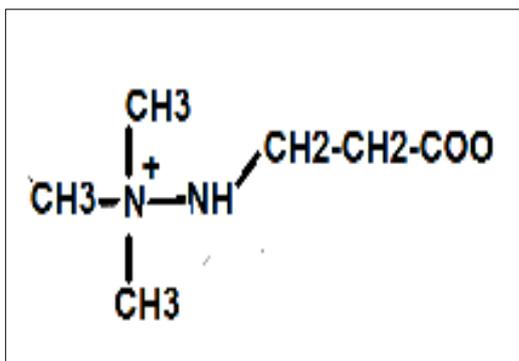


Figure 2: Chemical structure of meldonium.

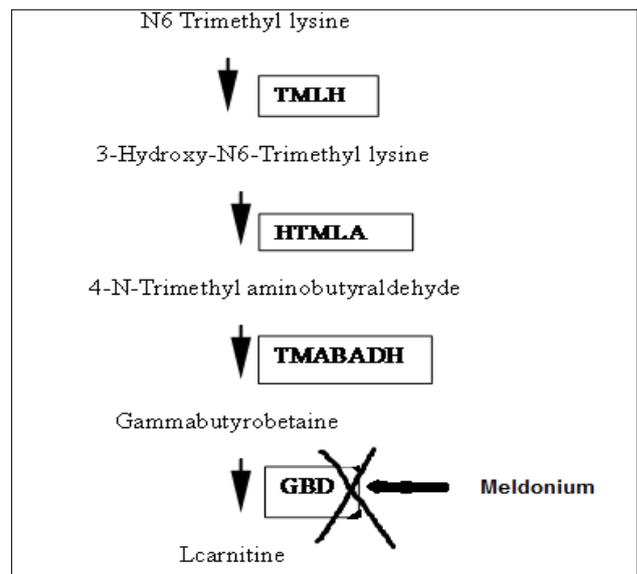
PHARMACOKINETICS OF MELDONIUM

Meldonium is a low molecular weight, water soluble compound and non-plasma protein binding in nature. Pharmacokinetic property of meldonium was observed in the healthy volunteers for single as well as multiple dose administrations. After single dose oral administration peak plasma concentration of drug was achieved in 2 hrs.

Its elimination half-life was found to be 18 hrs. after oral administration.⁷ It was observed that elimination half-life of meldonium increased after multiple consecutive intravenous administrations in compare to single intravenous dose (15.34±3.14 hours from 6.55±1.17 hrs).^{8,9} It could be, because meldonium exhibited nonlinear kinetics after multiple administrations leading to accumulation of drugs.¹⁰ Meldonium inhibits organic cation transporter-2 (OCT-2) which transports carnitine, the peculiar feature is that meldonium also transported by OCT-2 and because of which it gets accumulated in tissues and hence shows a long elimination time.¹¹

Mechanism of action

It decreases the L-carnitine level by inhibiting its synthesis and promoting its elimination. A quaternary amine, L-carnitine plays an important role in fatty acid oxidation by transporting fatty acid from cytosol to mitochondria, the site of beta oxidation.¹² Meldonium competitively inhibits the gamma butyrobetaine dioxygenase (gamma butyrobetaine hydroxylase or BBOX) a key enzyme which carried out the final step of L-carnitine synthesis (Figure 3).^{13,14}



TMLH- N5 Trimethyllysine hydroxylase
 HTMLA- 3-Hydroxy N5 Trimethyllysine aldolase
 TMABADH-4N- Trimethylaminobutyraldehyde dehydrogenase
 GBD- Gamma butyrobetaine dioxygenase

Figure 3: Meldonium inhibits the enzyme Gamma butyrobetaine dioxygenase, which converts gamma butyrobetaine to carnitine.

By acting as an inhibitor of carnitine transporter (OCTN2), it inhibits the reuptake of carnitine in kidney and promotes its elimination.¹⁵ Meldonium has a tendency to compete with L-carnitine for OCTN2.¹⁶ Meldonium also affects some other carnitine dependent enzymes like CPT1 (Carnitinepalmitoyltransferase-1), CrAT (Carnitine-OAcetyl Transferase) and CACT (Carnitine acylcarnitine translocase).¹⁷⁻¹⁹

PHARMACOLOGICAL ACTION AND THERAPEUTIC USES

Although meldonium was used initially to increase sperm motility and to enhance sexual performance, it is primarily known for its cardio protective effect. Studies have shown that, in different models of cardiovascular diseases it exerts cardio protective effect by inhibiting the L-carnitine level.^{20,21} In a study in knockout mice it was found out that it significantly reduces the development of atherosclerotic lesion in aorta and aortic sinus.²⁰ Similarly in a study of acute myocardial ischemia rat model, meldonium treatment for 10 days reduced the myocardial infarct size.²¹ It also prolongs the survival, prevents the cardiac remodeling and improves the energy states in rats with congestive heart failure following myocardial infarction.²² In guinea pig meldonium treatment attenuates hypoxic and reperfusion injury in the isolated heart.²³

Meldonium also have a significant role in metabolic diseases. In an animal model of diabetes (streptozotocin induced), it was found out that 6 weeks administration of meldonium reduced blood glucose and glycated hemoglobin level, improve glucose tolerance and prevented the development of diabetic associated neuropathy.^{24,25} In another experiment with rats; it was observed that meldonium prevents endothelial dysfunctional changes occur with diabetes mellitus.²⁶

In a clinical study, its role in post infarction period of CHF and diabetes mellitus was well demonstrated, where it tends to normalize the diastolic heart functions and increased the ejection fraction when given along with basic therapy.²⁷ Similarly in a clinical trial by Dzerve et al, it was seen that in patient of stable angina pectoris meldonium improves the exercise performance.²⁸

Although meldonium is used is not approved by USFDA but still it is widely used in Eastern European countries for multiple indications. It has been approved by different East European nations for use in angina pectoris, cardiomyopathy, abstinence syndrome in chronic alcoholism, bronchial asthma, obstructive bronchitis, hypertensive and diabetic retinopathies, neurodegenerative disorders, as immunomodulators, and many more.²⁹

MELDONIUM IN SPORTS

A data analysis of meldonium use by athletes in 2015 Baku European games revealed that 66 of 762 athletes found positive for this drug before or during the game.³⁰ Similarly in an analysis done by Gorgens et al, in 2015 in 8320 random urine sample of athletes from different discipline of sports, 182 were found to be positive for mildronate.³¹

To curb the increase misuse of this drug WADA had recently listed it as prohibited substance. WADA had issued a strong statement that “There is no doubt as to the

status of meldonium as a prohibited substance,” and warned athletes across the world about the implications of its use WADA has classed it as an S4 substance which comprises hormones and metabolic modulators according (5.3).^{1,32}

According to WADA report, 172 samples were found to be positive for meldonium since it has been announced as a banned drug, and this spans different sports and countries.³² This clearly speaks volume about its rampant misuse. The reason for this wide spread misuse of meldonium by athletes could be due to its low side effect profiles and its perceptible help in enhancing performance, it is assumed to increase the performance by increasing oxygen delivery to the peripheral tissue.³³

Despite such hue and cry about its misuse, experts are divided its regarding its direct role on exercise performance. So, more studies are required for a clear-cut picture to emerge.

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Ethical approval: Not required

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