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Meldonium – A High Potential Drug. Literature Review

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ABSTRACT

Introduction and purpose:

Meldonium is a long-established substance. Initially, the substance was only available in the former Soviet Union; now the drug can be obtained, for example, in Poland. Originally, its action was observed in the cardiovascular system as an antianginal drug. Today meldonium is already being used in ischaemic heart disease and chronic heart failure. This review provides exhaustive account of the pharmacological properties and clinical applications of the drug meldonium, with a particular emphasis on its biochemical effects, pharmacokinetics, and potential for performance enhancement in athletes.

Material and methods:

The literature available in PubMed and Google Scholar databases was conducted using the keywords.

Description of the state of knowledge:

Meldonium acts as a γ-butyrobetaine hydroxylase inhibitor, preventing de novo synthesis of carnitine and its absorption at the intestinal level. This leads to inhibition of ß-oxidation and activation of glycolysis, which is recognised as an anti-ischaemic and cardioprotective mechanism. The results of studies indicate the potential of this drug for the treatment of neurological and ischemic conditions. Meldonium is likely to improve performance in sport,

which led to the compound's inclusion on the World Anti-Doping Association's list of banned substances.

Conclusions:

Despite the high potential shown in studies to date, new, more thorough studies are needed to confirm the effectiveness of meldonium.

Keywords: Meldonium, Mildronate, heart failure, doping, professional athletes

Introduction

Meldonium was discovered at the Latvian Institute of Organic Synthesis over half a century ago [1]. It was invented as an animal growth promotion drug. Currently, the drug is mainly used in the former Soviet Union. Its systematic name is 3-(1,1,1-trimethylhydrazin-1-ium-2-yl)propanoate [2]. Research has explored its role in the treatment of various medical conditions, such as cardiovascular diseases, neurological disorders and metabolic disorders [3]. The original preparation of meldonium on the market is known as Mildronate. The drug has been known to athletes for a long time and there are indications of improved performance during exercise using this substance. Consequently, the World Anti-Doping Agency (WADA) included Mildronate on the lists of banned substances at the beginning of 2016 [4]. The main mechanism of action of meldonium is through the reduction of l-carnitine in tissues, thus altering the metabolism of fatty acids in the mitochondria [5].

Material and methods

The literature search was conducted via PubMed and Google Scholar. The search terms included "meldonium" and "mildronate" in conjunction with keywords such as "pharmacology," "heart failure," "ischaemic heart disease," "clinical trials," "performance enhancement," and "doping." The search was also limited to articles written in English and Russian.

The authors searched titles and abstracts and compared studies based on inclusion and exclusion criteria. Then they obtained the full text of the studies in question. The following criteria were subjected to in-depth analysis for each publication: pharmacokinetic parameters, mechanisms

of action, indications, effects on performance, safety and adverse effects. In addition, the authors translated and included Russian-language articles in the review.

Description of the state of knowledge

Mechanism of action of the drug

L-carnitine is a key substrate needed to transport long-chain fatty acids to the mitochondrion. There are used for oxidation and energy production [1,5]. The fatty acid (FA) is converted to the corresponding acyl-coenzyme A (Acyl-CoA) by long-chain acyl-coenzyme A synthetase (ACS) [5]. Subsequently, L-carnitine facilitates the transport of acyl-CoA into the mitochondria by conversion to the corresponding acylcarnitine via carnitine palmitoyltransferase-1 (CPT1). Then the resulting acylcarnitine is transported into the mitochondria by carnitine/acylcarnitine translocase (CACT) [5]. In the mitochondrial matrix, the acylcarnitine is converted back to the acyl-CoA by the action of the carnitine palmitoyltransferase-2 (CPT2), and then undergoes subsequent oxidation, producing the acetyl-CoA [5]. In glycolysis, glucose is metabolised to pyruvate, which is decarboxylated to acetyl-CoA by the pyruvate dehydrogenase complex (PDC). The acetyl-CoA formed by FA and glucose can be further metabolised in the Krebs cycle or converted to acetylcarnitine by carnitine acetyltransferase (CrAT) [5]. CrAT catalyses the formation of acetylcarnitine from acetyl-CoA and l-carnitine, thereby regulating the acetyl-CoA/free CoA ratio, which is detected by pyruvate dehydrogenase kinase (PDK), which inhibits PDC activity.

The precursor of l-carnitine is γ-butyrobetaine (GBB), which enters a four-reaction pathway. The final reaction is catalysed by γ-butyrobetaine hydroxylase. This enzyme is present in the kidneys, liver, and brain. This is step that is blocked by meldonium, resulting in no formation of l-carnitine [1]. Studies demonstrate that a four-week therapy leads to an average 18% decrease in plasma l-carnitine concentration and a 3-fold increase in urine concentration [4,6]. Blocking the formation of l-carnitine results increase in GBB concentrations, which is inextricably linked to the cardiovascular effects of meldonium [7]. Additionally, studies have demonstrated that meldonium can inhibit the enzyme organic cation / carnitine transporter 2 (OCTN2). The main function of this enzyme is to ensure high concentrations of organic cations including l-carnitine and GBB in tissues. Importantly, OCTN2 also ensures organic cation uptake in the ileum and reuptake in the kidney [8]. Inhibition of OCTN2 has been demonstrated to be a more efficacious approach to reduce l-carnitine availability and reduce myocardial infarct size [5]. Meldonium does not directly affect the CPT1 enzyme; however, due to the

reduced availability of l-carnitine, the activity of this protein is decreased. Meldonium is considered a weak inhibitor of the CRAT enzyme, but this has not been confirmed by in vivo studies. Meldonium has also been shown to inhibit the synthesis of trimethylamine (TMA), which is metabolised into l-carnitine by intestinal flora [5]. TMA is used to produce trimethylamino-N-oxide (TMAO). TMAO is harmful to the cardiovascular system [3]. It seems that TMAO and its metabolites are associated with insulin resistance and an increased risk of gastrointestinal cancer [9].

The whole process leads to a change in cellular metabolism from oxygen-intensive fatty acid oxidation to increased glucose consumption and enhanced adenosine triphosphate (ATP) generation efficiency, as well as protection of mitochondria from free fatty acid overload by reducing long-chain acylcarnitines, activating the utilisation of free fatty acids by mitochondria and redirecting fatty acid metabolism from mitochondria to peroxisomes [1,5]. In animal models it has been demonstrated, under the influence of meldonium, the glycogen content of muscle and liver decreases [10].

The impact on the tissues

Heart failure is a disease entity resulting from structural or functional abnormalities of the heart. This condition has many aetiologies. It is most commonly caused by a disruption in the filling or ejection of blood from the heart chamber, resulting in reduced cardiac output or increased intracardiac pressure [11]. These phenomena lead to a range of symptoms, including fatigue, dyspnoea, exercise intolerance and physical symptoms such as oedema around the ankles, crackling in the lungs [11]. There is scientific evidence for the efficacy of meldonium in the treatment of chronic heart failure. A study of 60 patients with chronic heart failure New York Heart Association (NYHA) class II to III, aged 43 to 70 years, who also had diabetes type 2, showed a reduction in NYHA symptoms, an increase in the distance covered in the 6-minute walk test and a trend towards normalisation of diastolic heart function and an increase in ejection fraction. Compared with control therapy, meldonium-treated patients showed statistically significant improvement in renal function, a significant decrease in triglyceride levels and total blood cholesterol levels. Hypoglycaemic properties were observed. The use of meldonium in primary therapy promotes the normalisation of vegetative homeostasis and improves quality of life [12]. Combination treatment with meldonium and lisinopril has been shown to be associated with improvements in quality of life, exercise capacity and peripheral circulatory mechanisms. In addition, it has a beneficial effect on health arterial and peripheral vasodilator capacity via nitric oxide(II) NO [13]. Meldonium also has the property of reducing the area of necrosis during myocardial infarction, as shown by studies in animal models. This

action is mediated by a reduction in l-carnitine concentration, concomitantly reduces fatty acid transport and maintains the integrity of the outer mitochondrial membrane in the heart mitochondria [14,15].

There are studies in patients with stable angina confirming the beneficial effect of meldonium on increasing exercise tolerance. The effect was found to be dose-dependent. The most effective and recommended dose of meldonium in combination with standard therapy was identified as 500 mg twice daily [16]. The effect of meldonium on patients with peripheral vascular disease has also been studied. The study confirmed that, after 24 weeks of treatment, patients with chronic vascular disease were able to walk a longer distance compared to the control group. Interestingly, the same study also showed that a four-week cessation of in meldonium intake does not lead to a loss of treatment effect and may be acceptable for long-term use [17].

Additionally, it has been hypothesised that meldonium has a beneficial effect on the myocardium in diabetic patients. The metabolism of glucose is reduced in the diabetic heart. Using hyperpolarised magnetic resonance imaging in an animal model, meldonium treatment led to a 3.1-fold increase in pyruvate dehydrogenase flow in diabetic and 1.2-fold non-diabetic group, indicating an increase in myocardial glucose metabolism. The present study, it was discovered, the improvement in cardiac function after ischaemia ex vivo is accompanied by an increase in pyruvate dehydrogenase in vivo. This was caused by meldonium increased the rate pressure product by 1.3-fold in control group and 1.5-fold diabetic group, resulting in faster convalescence post-ischaemia [18].

It is hypothesised that meldonium prevents the development of inflammation-induced right and left ventricular systolic dysfunction, which resembles cardiovascular complications in patients with SARS-CoV-2 infection. Studies were conducted in rats with right ventricular failure induced by pulmonary hypertension and in mice with inflammation-induced left ventricular (LV) dysfunction. Rats with right ventricular failure showed reduced right ventricular fractional area change (RVFAC) and hypertrophy. The administration of meldonium resulted in the attenuation of the development of right ventricular hypertrophy and increased RVFAC by 50%. Mice with inflammation-induced LV dysfunction had a reduced left ventricular ejection fraction (LVEF) by 30%. Meldonium treatment prevented the reduction in LVEF [19].

The potential of meldonium is also being considered in neurology. A study of a sample of 94 patients diagnosed with ischaemic stroke (mean age of patients 65.6±9.5 years) demonstrated that monthly meldonium therapy at a dose of 1000mg/d was associated with:

1. reduction in depression
2. reduction general and mental weakness
3. prevention of reduced activity during the follow-up period [1,20].

A recent study in rats showed that meldonium has beneficial effects as a neuroprotective drug during acute ischaemic stroke. It demonstrated:

1. a reduction in neurological deficit
2. a reduction in infarct volume
3. improvement of motor function after stroke
4. reduction of neuronal apoptosis in the cerebral cortex and hippocampus
5. improvement of mitochondrial structure and function of neurons exposed to stroke
6. increased antioxidant effect in cortex and hippocampus
7. improvement of mitochondrial morphology of the neuron after reperfusion with oxygen and glucose deprivation
8. inhibition of the Akt/GSK-3β pathway prevents neuronal death by mitochondrial-dependent apoptosis [1,21].

Other studies in animal models have demonstrated the potential benefits of meldonium in brain injury. The effect of this drug on the variability of three stress proteins was studied:
1. myeloperoxidase(MPO)-increased in injury, meldonium administration causes a decrease in MPO
2. Caspase-3 - increased, meldonium inhibits the increase of this protein
3. Superoxide dismutase:- decreased, meldonium abolishes its decrease.
In addition, brain tissues were examined histopathologically. The results demonstrated that after meldonium treatment, neurons are less damaged and have less damaged structure. This shows us meldonium as a potential drug to reduce inflammation and inhibit stress factors [1,22]. The researchers observed in a rat model of Parkinson's disease, that meldonium affects inflammation and apoptosis. Also they discovered in a mouse model of Alzheimer's, the administration of meldonium improved social recognition and spatial learning and a reduction the accumulation of β-amyloid peptides [1,4,23].

A further experiment was conducted on rats to ascertain the impact of meldonium on the progression of glaucoma. It proved that meldonium:

1. reduces intraocular pressure, which prevents the development of glaucoma
2. likely prevents fibrosis after surgical treatment of glaucoma
3. is potentially safe in eye drop form and has low penetration into the bloodstream

But the study also has its limitations:

1. it is difficult to determine whether nitric oxide(II) NO is responsible for the efficacy of meldonium
2. no studies assessing the effect of the drug on ocular structures

To summarise these reports, this is undoubtedly the beginning of research into the use of meldonium for topical treatment in ophthalmology [24].

Additionally, there have been reports indicating that meldonium may possess protective properties in the context of acute liver ischaemia, with antioxidant, anti-inflammatory, anti-arthritic and anti-apoptotic effects. Potential uses include preoperative preparation for liver resection or transplantation. Again, these data need to be verified in clinical trials [25].

Since 1 January 2016, WADA has included meldonium on its list of banned substances. To date, no high-quality clinical studies have been conducted to confirm the doping effects of meldonium on sports performance. Existing studies confirming the beneficial effects of this drug in cardiology and other medical fields may suggest that it has a supportive effect in sport. The efficacy of meldonium in popular use was evaluated at the 2015 European Games in Baku. 66 cases of meldonium use were identified of the 762 urine samples subjected to analysis, representing an incidence of 8.7%. 43 the athletes in this group did not admit to having taken the drug in the seven days preceding the survey. The athletes who had taken meldonium, the following results were observed:

- six athletes ranked first;
- five athletes took second place;
- two athletes came third.

In 15 of the 21 disciplines at the competition, athletes using this substance. These results indicate widespread use of this substance among athletes [1,26]. The impact of exhaustive exercise, in the form of swimming for one hour for 7 days was studied in rats. The activity resulted in mitochondrial DNA (mtDNA) damage, a reduction in glucose transporter type 4 (GLUT4) protein expression, an increase in dienes conjugates and a decline in reduced glutathione levels, which are stress proteins. In this study, meldonium was shown to have no effect on increase in strength and endurance, a smaller decrease in glutathione and 38% less mitochondrial DNA damage. Lung and brain mtDNA were less susceptible to exercise-induced oxidative damage. It can be concluded that meldonium did not affect mitochondrial biogenesis in the heart, it did not increase the expression of glucose transporter genes, but the amount of these genes was 3 times higher than in the control group, the expression level of genes responsible for fatty acid metabolism was unchanged. The administration of mildronate resulted

in a reduction in the level of oxidative stress, which is likely attributable to the inhibition of fatty acid transport within the mitochondria and an increase in the intensity of glucose oxidation. Lipid oxidation produces more adenosine triphosphate (ATP) than carbohydrates, but requires more oxygen per mole of ATP synthesised. In conclusion, meldonium does not alter metabolic mechanisms. but affects the proportion in which the metabolic pathways concerned predominate [27]. The current prohibition of meldonium makes, it is difficult to conduct research on what the effects of this substance actually are on an athlete's body. Despite, inconclusive evidence of meldonium's effect on enhancing athletic performance, it has been included on the list of banned substances. Once again, WADA's practice of designating a substance as a doping agent without conclusive testing is being challenged [28].

Additionally, the non-linear pharmacokinetics of meldonium pose diagnostic difficulties. The half-life of the drug following a single dose (up to 1,500 mg) has been observed to range from three to seven hours [4]. Meldonium is a small molecule and does not bind to proteins in plasma. Moreover, this drug is hydrophilic molecule. Typically, these characteristics were associated with very short elimination half-life. However, the chemical properties of meldonium are not so obvious. This drug is rapidly absorbed. The majority (78%) of the administered dose is delivered to the circulation and the plasma maximum concentration (Tmax) is 1-2 hours. The ingestion of food does not affect meldonium absorption, but prolongs Tmax. The majority of the metabolism of meldonium takes place in the liver. The enzyme BBOX is responsible for metabolising meldonium and leads to the formation of succinic acid and other metabolites. Meldonium is an inhibitor of OCTN2, so its affinity for this protein results in accumulation of this substance in tissues and an extremely long elimination time. Studies show that approximately 60% of meldonium is excreted via the kidneys. The elimination time of meldonium depends on treatment time and dose, and higher doses used by athletes may result in prolonged elimination time of meldonium due to accumulation. This information indicates that athletes and WADA must be aware of this atypical excretion profile. Probably the pharmacokinetics of meldonium were the cause of more than 100 adverse analytical results among meldonium-related athletes in early 2016 including world-class tennis player Marija Sharapowa [29,30].

Meldonium is characterised by the following side effects such as visual disturbances, burning sensations in the stomach or oesophagus, muscle cramps, loss of appetite and increased appetite dizziness, sluggishness or drowsiness depression, rapid heartbeat, tension-induced discomfort, allergic reactions [30].

Conclusions

We already know today that meldonium has potential in various different areas of medicine. Its multifaceted pharmacokinetic properties warrant further research into this substance. Despite the fact that meldonium is on the WADA list of banned substances, more research into its effects in sport is also required. In particular, research to date shows that the effects of meldonium are seen in all areas of ischaemia, inflammation and stress factors: heart, brain, eye, liver, muscle.

The potential of meldonium has can only be confirmed by scientific studies created on the global standards: multi-centre, on a large sample of patients and excluding as many confounding factors as possible. Such studies will allow us to accurately determine the pharmacokinetics, indications, contraindications, optimal dose of the drug in various indications. There is a need for extensive collaboration during such studies between physicians, laboratory professionals, and relevant organisations to establish a common consensus and ensure responsible use of meldonium while taking into account potential risks or ethical issues.

Disclosures

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