Meldonium (Mildronate): A Performance-Enhancing Drug?

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Meldonium (Mildronate, Mildronāts, Quaterine, MET-88) (Figure 1) is classified by the World Anti-Doping Agency (the regulatory body overseeing drug screening for international sporting events) as a performance-enhancing drug of the "metabolic modulator" class, a category that also includes insulin and trimetazidine. On 1 January 2016, the agency added meldonium to its Prohibited List; it had previously been among substances identified in the Monitoring Program. By 13 April 2016, the agency reported that approximately 170 athletes, including tennis premier Maria Sharapova, had tested positive for meldonium[1]; most of these screening results led to suspensions from competition. A majority of the offending athletes (including Sharapova) were of Russian nationality.

Meldonium is manufactured exclusively in Eastern Europe, principally by Grindeks in Riga, Latvia, and much of the biomedical research involving the compound comes from the Latvian Institute of Organic Synthesis, where it was originally synthesized. Meldonium is not FDA-approved in the United States, and was generally little-known in North America prior to the agency's rulings. The Western scientific community and lay press have questioned whether sufficient evidence exists to substantiate meldonium's actual performance-enhancing potential. Some athletes' legal representatives have also contended that their clients were the victims of excessively sensitive screenings. In response, the World Anti-Doping Agency announced that further study of meldonium's metabolism and excretion is needed. Many of the competitive bans may be subject to reconsideration.[2]

Meldonium is classified as a partial inhibitor of fatty acid oxidation; it binds to and competitively inhibits gamma-butyrobetaine hydroxylase, an enzyme necessary for carnitine biosynthesis. In a Latvian study, healthy human subjects treated with meldonium for four weeks experienced a mean decrease of 18% in plasma carnitine levels.[3] In the absence of carnitine, fatty acids cannot be transported into mitochondria and therefore cannot act as an energy source. It is speculated that the reduction in systemic carnitine produced by meldonium directly initiates a vasodilatory and antivasospastic cascade involving nitric oxide release.[4] Meldonium also increases the relative metabolic rate of glucose oxidation, a process with fewer oxygen demands than fatty acid oxidation; this might improve the function of cardiac myocytes under ischemic conditions.[5] This decrease in cardiac oxygen requirements is the primary factor speculated to underlie meldonium's alleged performance-enhancing potential.[6]

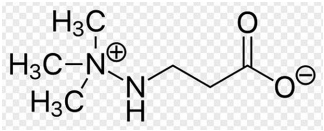

Figure 1. Chemical structure of meldonium (mildronate).

However, human data regarding the downstream biochemical and clinical consequences of meldonium-induced carnitine inhibition is minimal. Published studies on this topic have relied almost exclusively on animal and in vitro data. A Latvian study of 8 human volunteers found that meldonium decreased plasma levels of the carnitine metabolite trimethylamine nitrous oxide.[7] The authors suggest that this metabolite is associated with an increased risk of atherosclerosis, but no such association has been shown in humans. In Eastern Europe, meldonium is available without a prescription (Figure 2), and it has been used in the treatment for angina pectoris and myocardial infarction for approximately 40 years. Although animal studies have suggested that meldonium reduces the size of myocardial infarctions by as much as 30%,[8] this has also not been corroborated by English-language human data. More recently, meldonium has been used in the treatment of acute ischemic stroke. One animal study concluded that meldonium may facilitate vascular reactivity following cerebral ischemia; positive central nervous system effects, such as increased forced swim test performance, were also noted in animals.[9] Finally, one group reported ameliorative effects in a variety of animal neuropsychiatric disease models, including that of Parkinsonism. These authors suggested that meldonium altered the expression of several proteins associated with neuroinflammation, though the applicability of these findings to humans is unclear.[10,11] The above-cited authors, all Latvian, have recommended that meldonium be investigated or used for the treatment of schizophrenia, Alzheimer's dementia, and "physical and psycho-emotional overexertion." These recommendations and extrapolations, however, are not supported by clinical data.

Figure 2. Meldonium (mildronate) 500 mg capsules, as offered on a Russian web site at a cost of approximately U. S. $1.00 per capsule. The product is manufactured by Grindeks in Riga, Latvia, and is available without prescription.

There is minimal English-language data (i.e., publications indexed in the PubMed database) regarding the safety and efficacy of meldonium as a therapeutic agent in patients with cardiovascular or neurological disorders, or as a performance-enhancing drug in otherwise healthy individuals. A randomized, controlled trial found that meldonium significantly and dose-dependently increased exercise tolerance in patients with chronic cardiovascular disease (n = 512; mean age approximately 60 years). However, the absolute increases in mean tolerance were in fact small (less than 1 minute in all cases).[4] A small, open-label trial of meldonium in the Republic of Georgia (n = 16) reported improved measures of cardiac function in patients with congestive heart failure.[12] It was not clear, however, whether the patients in the treatment group experienced better clinical outcomes. A randomized, controlled trial (n = 227) done in China concluded that meldonium is comparable in safety and efficacy to cinepazide in the treatment of acute cerebral infarction.[13] It should be noted that cinepazide itself is not FDA-approved and has been withdrawn from the French and Spanish formularies in past decades. There is essentially no English-language data regarding the effect of meldonium on exercise tolerance or cardiovascular function in healthy subjects or trained athletes.

Pharmacokinetic studies of meldonium indicate that its elimination half-life after single doses (up to 1500 mg) is in the range or 3 to 7 hours.[14–16] However, some data indicates a prolongation of half-life to the range of 15 hours in the washout phase after exposure to multiple doses,[15,16] suggesting nonlinear kinetics. The implications of these parameters for drug testing of athletes, however, have not been established. The duration of persistence of a positive screening result following discontinuation of meldonium is not known. The urine testing procedures target intact meldonium,[17] indicating that urinary excretion of the intact compound accounts for at least a component of net clearance.

In sum, there is minimal evidence from North America and Western Europe regarding meldonium's role in the treatment of disease, or whether it can produce meaningful performance enhancement in highly trained athletes. Extrapolations and recommendations based in in vivo or animal data should be weighed critically. There is also insufficient evidence to establish the temporal sensitivity of currently-used analytic screening procedures to detect meldonium use in the context of athletic competition.[17] As such, the athletes' claims described above cannot be refuted. Further study is necessary to determine meldonium's clinical effects, if any, upon trained athletes, as well as to determine what conclusions may be drawn from positive screening results. Given that meldonium is not used clinically, experimentally, or recreationally in Western countries, satisfactory evidence seems unlikely to emerge in the near future.

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