Letter to the Editor

Meldonium (Mildronate): Primum non nocere

Meldonium (Mildronate) is used as a cardioprotective drug; however, it has not been approved for the use anywhere outside the former Soviet Union (SU) [1]. The action mechanism is supposed to be based on the carnitine (t-carnitine) lowering effect also in muscular and cardiac tissues [2]. The carnitine deficiency is known to be accompanied by muscle ache, fatigue, muscular weakness, and cramps at exertion; it can induce hypoketotic hypoglycemia, which is potentially unfavorable both for the nervous and muscular functions. In the works by the same research group as [2], the oral administration of Meldonium to healthy volunteers at the recommended dose 1 g/day for 4 weeks brought about a significant lowering of plasma carnitine by 18%. Administration of meldonium to rats at a dose 100 mg/kg for 14 days induced a 69% decrease in t-carnitine concentration in the heart tissue. In a series of studies from the former SU, efficiency of meldonium has been uniformly confirmed in cardiac insufficiency, myocardial infarction, stroke and other conditions also in the geriatric settings. In the author’s opinion, data trimming cannot always be excluded. Considering potential decrease in the muscular (including cardiac) function in conditions of carnitine deficiency, meldonium could have contributed to a further decrease in the cardiac function especially in conditions of decompensation. There is a considerable body of evidence that carnitine exerts a cardioprotective effect in cardiomyopathy, lessens infarct size, prevents arrhythmias and improves survival in myocardial infarction, increases exercise tolerance in angina and heart failure etc. For example, in a double-blind trial, 2330 patients with myocardial infarction were randomly assigned to receive placebo or carnitine. The mortality rate was significantly lower in the carnitine group [3]. Administration of carnitine reduced ischemic myocardial injury in experimental models. In rats, carnitine protected against development of infarct-like myocardial necrosis induced by isoproterenol. Supplementation of the myocardium with carnitine is assumed to result in a prevention of the loss of high-energy phosphate stores, ischemic injury, and improved heart recovery on reperfusion [4]. Moreover, carnitine depletion might interfere with the function of nervous and endocrine systems, where the substance participates in feedback mechanisms [5]. In the article by Dambrova et al. it is written: “t-Carnitine biosynthesis enzyme γ-butyrobetaine hydroxylase and carnitine/organic cation transporter type 2 (OCTN2) are the main known drug targets of meldonium, and through inhibition of these activities meldonium induces adaptive changes in the cellular energy homeostasis. Since t-carnitine is involved in the metabolism of fatty acids, the decline in its levels stimulates glucose metabolism...” [2] In the author’s opinion, induction of adaptation by additional load or “glycolysis training” might be discussed for stable chronic conditions or healthy athletes, which is a topic for a separate review. However, training is hardly applicable for acute myocardial infarction, heart failure, in geriatrics, i.e. in conditions of decompensation or close to it, where any additional load may be harmful. This seems to be true also for extreme loads in athletes. It has been reasonably assumed that the World Anti-Doping Agency (WADA) decided to add meldonium to the Prohibited List because of the risk that it carries for athletes [1]. Apparently, subconjunctival injections of meldonium, applied in the former SU, should be discouraged. A benefit from a short-term concentration increase of this substance in the orbital tissues can hardly be understood, while the procedure bears a risk of hematoma and infection. Parabulbar injections of carcine and taurine, seen to be complicated by hematomas, have been commented previously. Considering the above, meldonium is probably a placebo with potential adverse effects (pseudo-placebo). If in doubt, it can be verified in reliable experiments.

References


Sergei V. Jargin
Peoples’ Friendship University of Russia,
Clementovski per 6-82, 115184 Moscow, Russia
E-mail address: sjargin@mail.ru

20 September 2016
Available online xxx