Meldonium

Ruth Cordiner
MBChB, MRCP, Specialty Trainee in Diabetes and Endocrinology, Glasgow Royal Infirmary, Glasgow, UK

Correspondence to:
Dr Ruth Cordiner, Department of Diabetes, Endocrinology & Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK; email: ruth.cordiner@nhs.net

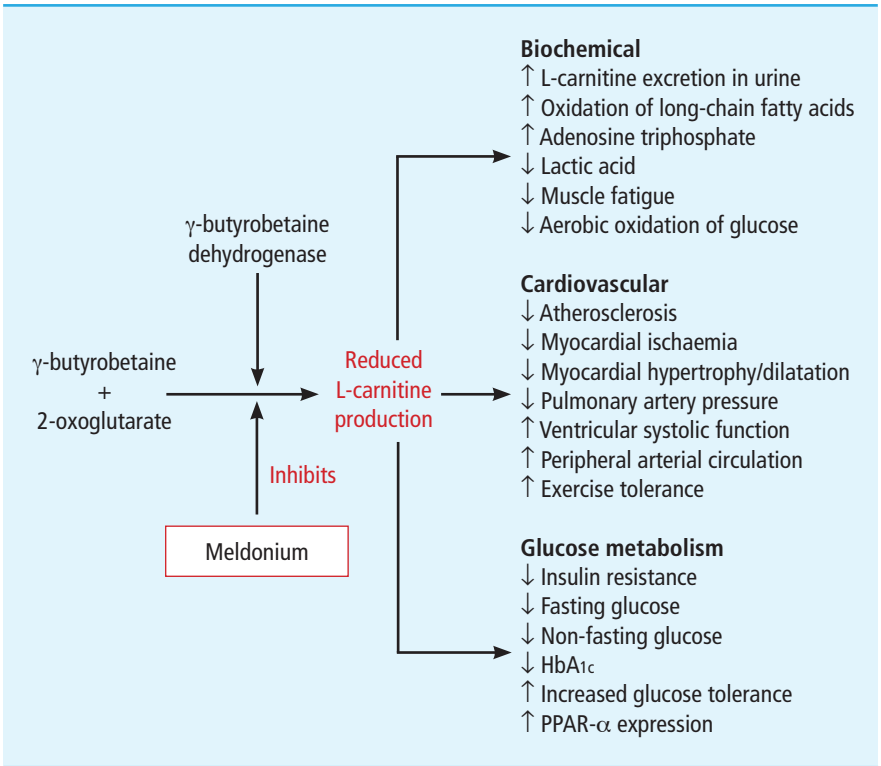

Figure 1. Meldonium reduces L-carnitine production through competitive inhibition of γ-butyrobetaine dehydrogenase. Reduced plasma L-carnitine levels impact biochemically, as well as physiologically on the cardiovascular system and glucose metabolism

Introduction

Meldonium is an anti-ischaemic drug, originally developed in the 1970s by the Latvian Institute of Organic Synthesis as a growth-promoting agent for animals. It is not approved in Europe or the USA, but is registered for human use in Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Ukraine, Uzbekistan and Russia, as a cardioprotective agent in coronary artery and cerebrovascular disease. Other clinical indications include neurological, metabolic, pulmonary and ophthalmological disease.

Meldonium was added to the World Anti-Doping Agency (WADA) 'prohibited list' in January 2016 following a year on its monitoring programme. WADA has classed it as a 'metabolic modulator used by athletes to enhance performance'. Meldonium has received media scrutiny following the alarming prevalence of doping by athletes at the Baku European Games 2015 and most notably Maria Sharapova's suspension by the International Tennis Federation following a failed drugs test at the Australian Open.

Pharmacology

Meldonium (trimethylhydrazinium propionate) regulates energy metabolism through reduction of levocarnitine (L-carnitine); (Figure 1). L-carnitine is found naturally in milk and meats, and synthesised from lysine and methionine. It is a water-soluble amine, vital in mitochondrial oxidation of fatty acids and energy production in skeletal muscle. Interestingly, it is marketed in the USA as a dietary supplement, or added to energy drinks to improve athletic performance.[1] However, there is no good evidence to support this.

L-carnitine transports activated long-chain fatty acids from the cytosol into the mitochondria, where α-oxidation and adenosine triphosphate (ATP) synthesis take place. Meldonium inhibits γ-butyrobetaine hydroxylase and fatty acid transportation by L-carnitine,

overall reducing L-carnitine levels in tissue and plasma. The reduction of L-carnitine causes energy synthesis to shift from highly oxygen consuming fatty acid oxidation, to increased glucose metabolism. Aerobic glucose oxidation is more efficient, consuming far less oxygen, and increases the effectiveness of ATP generation. It also appears to increase glucose uptake leading to speculation of a role in the management of diabetes mellitus.

Meldonium protects mitochondria from overload of free fatty acid (FFA) through reduction of long-chain acylcarnitines, increasing mitochondrial FFA utilisation and the redirection of FFA metabolism from the mitochondria to the peroxisomes. In ischaemic conditions, meldonium appears to restore the balance between cellular oxygen supply and demand, and prevents impairment of ATP transport.

Trials of efficacy and safety

Meldonium efficacy studies are predominantly in Russian, with translated abstracts reporting positive effects in cardiovascular disease.[1] Meldonium trials in Baltic countries observed improvement in ventricular systolic function, inhibited myocardial hypertrophy and dilatation, decreased pulmonary artery pressure, increased peripheral circulation and stress tolerance.[1]

The only English language study is a prospective, randomised, double-blind, placebo controlled phase 2 trial, which assessed 'the efficacy of various doses of meldonium in combination with standard therapy on exercise tolerance of patients with stable angina pectoris'.[2] It evaluated 512 patients, from 72 centres in four countries, with coronary artery disease and positive exercise testing for ischaemia. The primary endpoint was change in exercise time on bicycle ergometry from baseline to week 12. Secondary endpoints were changes in maximum achieved load and time to onset of angina. Patients were assigned to groups receiving standard therapy plus meldonium at different doses, versus one group of standard therapy plus placebo.[2] The mean change in exercise time in meldonium 100mg and 300mg groups was -2.12±108.45 and 11.48±62.03 seconds, respectively. The placebo group observed a mean change of -7.10±81.78 seconds. Meldonium 1000mg showed a statistically significant increase in mean change in total exercise time (35.18±53.29 seconds, p=0.002). A non-statistically significant increase was observed with 3000mg. Similar outcomes in secondary endpoints were observed. The concluded most effective dose of meldonium was 500mg twice daily in combination with standard therapy.

Adverse effects were headache, agitation, tachycardia, allergic skin reactions and dyspepsia. Serious adverse effects have not been found; however, no long-term studies on safety and efficacy of meldonium have been published. The mild adverse effect profile, combined with performance enhancing potential, may be the reason why meldonium is used for doping in athletes.

Evidence for use in diabetes

Due to its role in fatty acid and glucose metabolism, meldonium has potential benefit in diabetes mellitus. So far, Latvian trials in animal models have supported this hypothesis; however, there are no high quality clinical trials in humans. Liepinsh *et al.* studied the protective effects of meldonium in an experimental model of type 2 diabetes (T2DM) in rats, observing decreased L-carnitine concentrations in rat plasma, reduced fasting and non-fasting glucose, improved glucose tolerance and reduced HbA_{1c}.[3]

Studies have observed meldonium to reduce skeletal muscle insulin resistance in T2DM via regulation of α-oxidation of fatty acids and efficient mitochondrial ATP production. In a mouse and human myotube study, meldonium reversed acylcarnitine-induced insulin resistance. A Latvian trial studied the antidiabetic effects of meldonium alone or in combination with metformin in obese rats.[4] Zucker rats were treated with oral meldonium (200mg/kg), metformin (300mg/kg), or combination daily for four weeks. Primary outcomes were weight gain and plasma metabolites of glucose metabolism. Heart and liver tissue were examined for expression of peroxisome proliferator-activated receptor (PPAR)-α and PPAR-γ. Each treatment reduced blood glucose concentration during fed and fasted states by 1–2mmol/L.

Key points

- Meldonium has received media and medical scrutiny following its inclusion on the World Anti-Doping Agency's prohibited list as a performance enhancing drug
- The evidence base for potential benefit in cardiovascular disease and diabetes is limited to animal studies from Baltic countries where it is approved for use
- Before clinical approval can be justified, further large-scale clinical trials of efficacy, safety and long-term outcomes are required

Meldonium and metformin reduced plasma insulin concentration by 31% and 29% respectively, with a 47% reduction in fed insulin concentration when used in combination. Combination therapy significantly decreased weight gain by 19%. Increased expression of PPAR-α was measured in heart tissue and PPAR-γ in both heart and liver tissue.

Discussion

Meldonium has potential clinical benefit in cardiovascular disease and diabetes, which can be ascribed to its reduction of L-carnitine causing inhibition of α-oxidation, enhanced efficient aerobic glucose metabolism and ATP production. Evidence on efficacy, safety and long-term outcomes is limited, particularly following WADA prohibition of meldonium as a performance-enhancing drug. The main clinical trials for meldonium are from Baltic countries, and predominantly in Russian. Outcomes in animal models suggest possible benefit in reducing insulin resistance and improved glycaemic control in T2DM. However, these studies are without the high-level evidence base, regulation and registration processes required of clinical trials conducted in the Western world. Large-scale clinical trials of meldonium or molecularly similar agents are required in order to further investigate its potential clinical benefit.

Declaration of interests

There are no conflicts of interest.

References

References are available online at www.practicaldiabetes.com.

Meldonium

References

1. Schobersberger W, *et al*. Story behind meldonium – from pharmacology to performance enhancement: a narrative review. *Br J Sports Med* 2016 July 27. doi: 10.1136/bjsports-2016-096357. [Epub ahead of print.]
2. Dzevre C; MILSS I Study Group. A dose-dependent improvement in exercise tolerance in patients with stable angina treated with Mildronate. *J Med Chem* 2014;57:2213–36.
3. Liepinsh E, *et al*. Protective effects of mildronate in an experimental model of type 2 diabetes in Goto-Kakizaki rats. *Br J Pharmacol* 2009;157:1549–56.
4. Liepinsh E, *et al*. Anti-diabetic effects of Mildronate alone or in combination with metformin in obese Zucker rats. *Eur J Pharmacol* 2011;658:277–83.