Use of Meldonium (Mildronate) in the Combined Treatment of Arterial Hypertension in Patients with Ischemic Heart Disease and Its Effects on Cardiac and Vascular Morphofunctional Status

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Abstract

Background. This article examines the effects of long-term combined treatment with Mildronate (meldonium) and the angiotensin-converting enzyme inhibitor ramipril on endothelial function and the morphofunctional state of the heart and blood vessels. Cytoprotective agents that shift cellular energy metabolism away from fatty-acid oxidation toward the more oxygen-efficient use of glucose have become increasingly common in cardiology. Because left-ventricular and vascular-wall remodeling is accompanied by activation of free-radical oxidation and disturbances of energy metabolism, and because many antihypertensive effects are mediated through nitric oxide and vascular endothelial function, adding Mildronate to the treatment of hypertension in patients with ischemic heart disease appears pathophysiologically justified.

Aim. To determine the effect of Mildronate added to antihypertensive therapy with an angiotensin-converting enzyme inhibitor on left-ventricular hypertrophy, systolic and diastolic function, common carotid artery intima-media thickness, and endothelium-dependent vasodilation of the brachial artery in patients with hypertension and ischemic heart disease.

Materials and methods. Fifty patients with stage II, moderately severe hypertension were randomized into two groups of 25. Both groups received ramipril monotherapy for 3 weeks. Beginning on day 21, the intervention group also received oral Mildronate 500 mg twice daily. Mildronate was administered continuously for the first 6 months and subsequently in 2-month courses separated by 2-month treatment-free intervals. Total follow-up was 24 months. The control group received ramipril alone.

Results. Adding Mildronate to ramipril was associated with favorable changes in the severity of left-ventricular hypertrophy, systolic and diastolic function, endothelial dysfunction, and common carotid intima-media thickness. The effects were most pronounced with long-term systematic use.

Keywords: arterial hypertension; ischemic heart disease; cytoprotective agents; meldonium; Mildronate; ramipril.

Introduction

The treatment of essential hypertension remains an important challenge in modern health care. Elevated blood pressure is commonly accompanied by marked endothelial dysfunction. The resulting imbalance between endothelium-dependent vasodilator and vasopressor systems aggravates hypertension and worsens peripheral and central hemodynamics. This is a key factor in the development of the hypertensive heart, including left-ventricular myocardial hypertrophy and diastolic and systolic dysfunction. Endothelial dysfunction may also substantially reduce the effectiveness of antihypertensive agents whose pharmacological effects are mediated through endothelial regulation of vascular tone.

Another important pathogenetic factor contributing to the progression of hypertension is increased free-radical oxidation. High peroxide concentrations accelerate nitric oxide degradation, lowering its bioavailability and reducing the vasodilator capacity of the vascular endothelium [1-6].

Cytoprotective agents have become increasingly used in cardiological practice. Their pharmacodynamics include shifting cellular energy metabolism from fatty-acid oxidation toward predominant glucose utilization, which is more economical in terms of oxygen consumption. Optimization of cellular energy metabolism may favorably influence endothelial function. Cytoprotective agents also have moderate antioxidant properties and may reduce the adverse effects of oxidative stress on the vascular endothelium [7-9].

The literature contains numerous reports of effective cytoprotective therapy as part of combined treatment for hypertension. In hypertensive patients, cytoprotective agents have been reported to favorably affect lipid peroxidation, endothelial function, blood pressure and its circadian profile, and cardiac and vascular status [10-15].

Among these agents, clinically relevant effects have been described for Mildronate - 3-(2,2,2-trimethylhydrazinium) propionate dihydrate, also known as meldonium. The drug inhibits carnitine synthesis and promotes nitric oxide production through accumulation of gamma-butyrobetaine, which stimulates acetylcholine receptors. It limits the transport of fatty acids into mitochondria and stimulates hexokinase and pyruvate dehydrogenase, thereby promoting aerobic glucose oxidation and preventing acidosis [8,16-25]. During Mildronate treatment, mitochondrial concentrations of intermediate fatty-acid metabolites do not rise; such intermediates may otherwise serve as precursors of toxic lipid peroxides and activate free-radical processes [26].

Because remodeling of the left-ventricular myocardium and vascular wall is accompanied by oxidative activation and altered energy metabolism, and because many antihypertensive effects depend on nitric oxide and endothelial function, the use of Mildronate in the combined treatment of hypertension in patients with ischemic heart disease appears justified.

Aim

To determine the effects of Mildronate, when added to antihypertensive therapy with an angiotensin-converting enzyme inhibitor, on the severity of left-ventricular hypertrophy, left-ventricular systolic and diastolic function, common carotid artery intima-media thickness, and endothelium-dependent brachial-artery vasodilation in patients with essential hypertension and ischemic heart disease.

Materials and Methods

Fifty patients (33 men and 17 women) with stage II, moderately severe essential hypertension were followed. Their ages ranged from 42 to 63 years, and the duration of hypertension ranged from 4 to 9 years. Before enrollment, all participants underwent a comprehensive examination to determine cardiovascular risk, target-organ damage, concomitant disease, and possible secondary hypertension.

All enrolled patients had left-ventricular hypertrophy and ischemic heart disease with stable exertional angina of functional class I. Cardiovascular risk was classified as very high. Most patients had hypercholesterolemia that was controlled to target levels by diet and moderate-dose statin therapy (atorvastatin 20 mg/day). Patients with marked hypercholesterolemia (total cholesterol above 6.2 mmol/L) were excluded. Antihypertensive drugs were withheld for at least 10 days before treatment began.

Patients were randomized into two groups of 25. For the first 3 weeks, both groups received ramipril monotherapy at 5-10 mg/day for dose titration and blood-pressure control. Daily dosing was determined by the antihypertensive response and achievement of target blood pressure. Clear lack of efficacy of ramipril was an exclusion criterion.

Beginning on day 21, the intervention group additionally received oral Mildronate 500 mg twice daily. The drug was given continuously for the first 6 months, followed by 2-month courses separated by 2-month treatment-free intervals. Total follow-up was 24 months. The control group continued ramipril monotherapy.

Echocardiography (Toshiba Xario SSA-660A, Japan) was performed before treatment and at 6 and 24 months. The left-ventricular mass index (LVMI), the ratio of peak early to late transmitral filling velocities (E/A), and left-ventricular ejection fraction (LVEF) were measured. Doppler vascular ultrasonography assessed endothelium-dependent brachial-

artery vasodilation during reactive hyperemia and common carotid intima-media thickness (CIMT) [27,28]. Brachial-artery diameter was measured before occlusion and 60 seconds after release of compression [29].

Results and Discussion

The groups did not differ significantly in any measured baseline parameter. During the 2-year follow-up, 7 patients withdrew from the control group: 1 developed a small focal myocardial infarction, 3 experienced disease progression, and 3 developed concomitant conditions requiring changes in therapy. Four patients withdrew from the intervention group: 2 developed concomitant diseases, and 2 required combined antihypertensive therapy with two or three agents.

In the intervention group, the initial ramipril dose was reduced in 5 patients and increased in 4. In the control group, ramipril dose escalation was required in 7 patients and dose reduction in 3.

Endothelial dysfunction is an important marker of vascular damage. It predicts angiopathy and atherosclerosis and influences the effectiveness of antihypertensive drugs whose actions are mediated through nitric oxide. At baseline, all patients showed impaired endothelial nitric oxide generation, reflected by reduced endothelium-dependent brachial-artery vasodilation.

By month 6, flow-mediated dilation of the brachial artery had increased significantly in both groups: 2.7-fold with ramipril alone and 3.3-fold with ramipril plus Mildronate (Figure 1). During subsequent follow-up, no further increase was observed in the control group. In the intervention group, flow-mediated dilation at month 24 was 3.9 times the baseline value. The number of patients with an inadequate (<10%) increase in brachial-artery diameter during reactive hyperemia was 8 at month 6 and 7 at month 24 in the control group, versus 6 and 3, respectively, in the ramipril-plus-Mildronate group.

Thus, both ramipril monotherapy and combined treatment corrected endothelial dysfunction, but the greatest effect, particularly with long-term use, was observed with the combination of ramipril and Mildronate.

Table 1. Changes in selected echocardiographic parameters during treatment (mean ± standard error)

Treatment	Parameter	Baseline	Month 6	Month 24
Ramipril	LVMI, g/m²	144.2 ± 3.1	141.9 ± 3.9	131.3 ± 3.1*
	E/A	0.97 ± 0.03	1.21 ± 0.03*	1.24 ± 0.04*
	LVEF, %	62.7 ± 1.8	64.7 ± 1.2	66.2 ± 1.1*
Ramipril + Mildronate	LVMI, g/m²	142.8 ± 2.5	134.7 ± 3.0*	124.3 ± 2.9*
	E/A	0.98 ± 0.03	1.29 ± 0.03*	1.59 ± 0.04*
	LVEF, %	62.4 ± 1.8	66.4 ± 1.0*	67.9 ± 1.1*

* $p < 0.05$ compared with baseline.

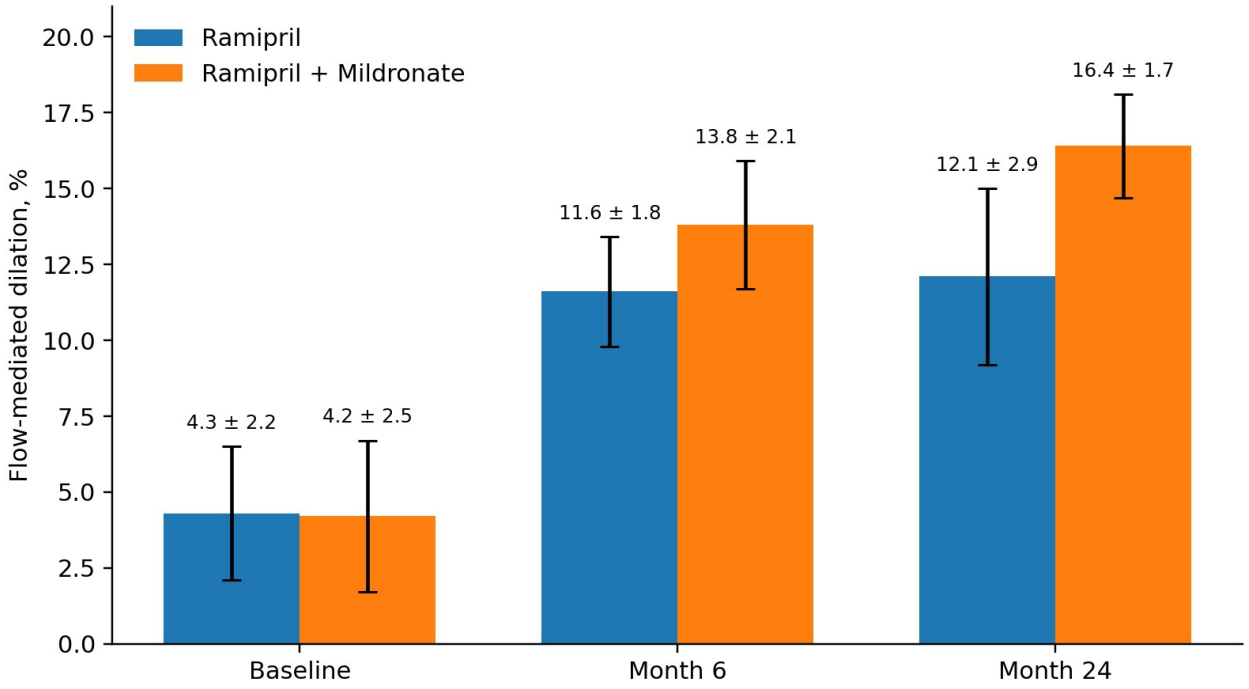

Figure 1. Endothelium-dependent (flow-mediated) vasodilation of the brachial artery during reactive hyperemia in patients with hypertension during treatment (mean ± standard error). Values were redrawn from the published figure.

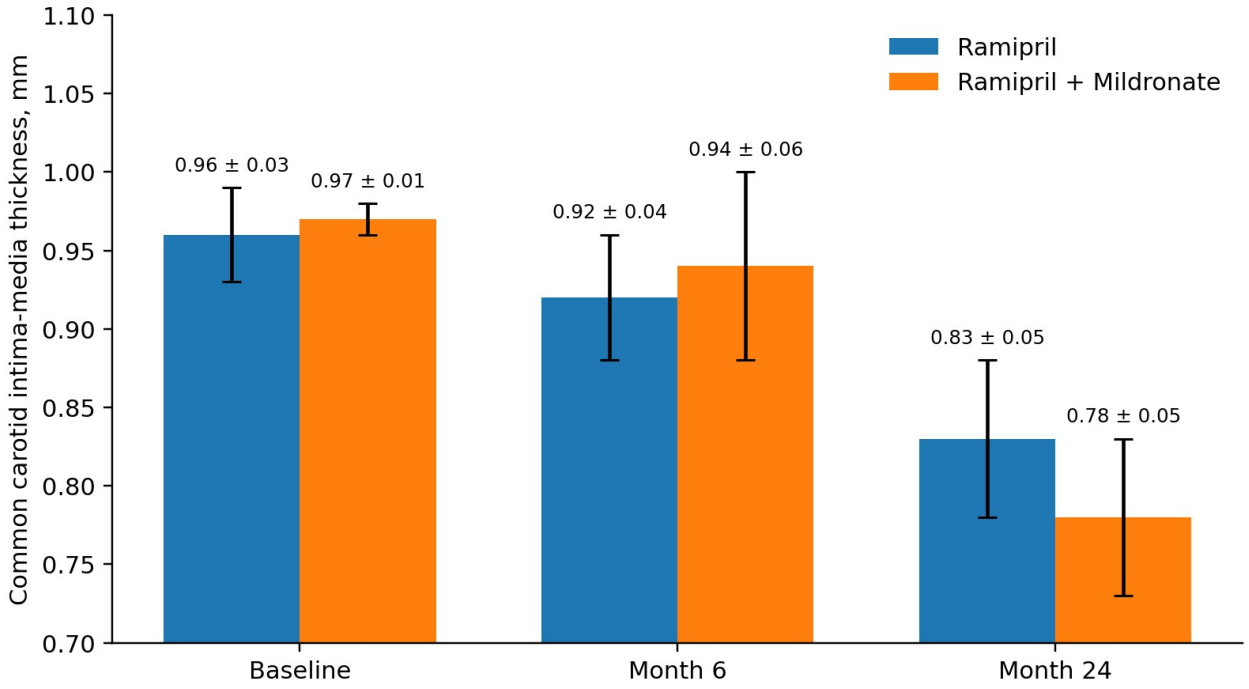

Figure 2. Common carotid artery intima-media thickness in patients with hypertension during treatment (mean ± standard error). Values were redrawn from the published figure.

CIMT characterizes arterial target-organ injury. By month 24, CIMT had decreased in both groups, probably because angiotensin-converting enzyme inhibition corrected endothelial dysfunction, a leading contributor to vascular remodeling [30]. The reduction was significantly greater with ramipril plus Mildronate (19.6%) than with ramipril alone (13.3%). The authors attributed this difference to a favorable effect of Mildronate on the vascular endothelium and a cytoprotective effect on vascular smooth-muscle cells [26,31].

The E/A ratio increased significantly in both groups by month 6. The increase was greater in patients receiving ramipril plus Mildronate (31.6%) than in those receiving ramipril alone (24.7%). By month 24, E/A had not increased further in the control group, whereas in the intervention group it was 62.2% above baseline.

In the intervention group, LVMI had decreased by 5.7% at month 6. At month 24, LVMI was significantly lower than baseline in both groups, but the reduction was greater with combined treatment (13.0%) than with ramipril monotherapy (9.0%).

LVEF increased significantly by month 6 in the ramipril-plus-Mildronate group (6.4%). At month 24, the reported increase was 8.8%. In the control group, the increase was smaller and was reported as 4.0%.

Angiotensin-converting enzyme inhibitors are known to improve systolic and diastolic dysfunction and reduce left-ventricular hypertrophy [31-33]. Adding Mildronate to antihypertensive therapy may enhance the favorable effects of ramipril on intracardiac hemodynamics through cytoprotection of cardiomyocytes [24,26,34-37]. Previous studies have reported efficacy of cytoprotective agents in patients with ischemic heart disease and left-ventricular systolic or diastolic dysfunction, potentially through favorable effects on cellular energy metabolism [35-37].

The antioxidant and endothelium-protective properties of Mildronate may also be important. By reducing free-radical oxidation and increasing nitric oxide bioavailability, the drug may help restore endothelial function, promote reverse remodeling of the vascular wall, and reduce afterload [38]. The results of the present study support an endothelium-protective effect of Mildronate when used with ramipril [39].

Conclusion

The findings suggest that adding the cytoprotective agent Mildronate to ramipril may be useful in patients with essential hypertension and ischemic heart disease. Combined treatment favorably affected the severity of left-ventricular hypertrophy, systolic and diastolic function, endothelial dysfunction, and common carotid intima-media thickness. The effects of Mildronate were most pronounced with long-term systematic use.

Conflict of interest. The authors declared no conflicts of interest.

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