A placebo-controlled, double-blind, randomised trial of magnesium-pyridoxal-5′-phosphate-glutamate for hypercholesterolaemia and other clinical–chemical risk factors of cardiovascular disease in a primary care setting

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Abstract Background: Lipid-lowering drugs are extensively used in primary care to reduce the risk of cardiovascular disease (CVD). Apart from high total cholesterol (TC), several other clinical–chemical variables are associated with the risk of CVD. Magnesium-pyridoxal-5′-phosphate-glutamate (MPPG) has been found to have a positive influence on TC levels and other clinical–chemical values in some selected populations. Objectives: To assess, in a general practice (GP) setting, the efficacy and clinical effectiveness of MPPG in the treatment of clinical–chemical risk factors for CVD. Design: Randomised double-blind, placebo-controlled, clinical trial, lasting 12 months. Patients: Adults (25–66 years) in an average Dutch village population with serum cholesterol levels between 7.0 mmol/l and 9.9 mmol/l.

Intervention: Subjects were assigned at random to treatment with MPPG (3x150 mg daily) or placebo. Clinical–chemical parameters were assessed at 1, 3, 6, 9 and 12 months (t_1, t_2, t_3, t_4, t_5). Efficacy was measured at t_2. Long-term effect (clinical effectiveness) was measured by combining the results at t_2, t_3, t_4 and t_5 (t_2−5).

Outcome measures: TC (primary), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides, apolipoprotein-A1 (Apo-A1), apolipoprotein-B100 (Apo-B), fibrinogen and lipoprotein a [Lp(a), secondary].

Results: No statistically significant differences in the efficacy and effectiveness of TC were found between the MPPG group and the placebo group. The same was demonstrated for the other clinical–chemical values, except for LDL-C (effectiveness, \( P = 0.04 \)).

Conclusions: Efficacy and effectiveness of MPPG are too poor to be of relevance for application as a lipid-lowering drug in GP.

Key words Magnesium-pyridoxal-5′-phosphate-glutamate • Hypercholesterolaemia • Cardiovascular disease

Introduction

Hypercholesterolaemia has been established as one of the major risk factors for cardiovascular disease [1, 2]. The risk of myocardial infarction in middle-aged, apparently healthy men can be reduced by lowering cholesterol levels [3, 4, 5].

The Dutch guidelines, issued in 1998, recommend as medication of first choice the hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) [6]. This choice is mainly based on their potent action on total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C) levels. Although the effects of the individual statins differ, they generally also exert an effect on apolipoprotein-B100 (Apo-B) and to a lesser extent on high density lipoprotein-cholesterol (HDL-C), apolipoprotein-A1 (Apo-A1) and triglycerides [5, 7, 8, 9, 10, 11, 12]. As such, the statins are more potent than the older type cholesterol-lowering drugs such as niacin, the bile acid sequestrants and the fibrates.

Although they are considered safe drugs for prevention, all of these have their side effects. The statins must not be prescribed in cases of liver and kidney dysfunction, during pregnancy and lactation or to women with insecure contraception. Most side effects are gastrointestinal [5, 7, 8, 9, 10, 11, 12].

During the same period in which the statins were being developed, studies using scientific standards were
performed with magnesium-pyridoxal-5'-phosphate-glutamate (MPPG), a vitamin B6 derivative [13, 14, 15]. Several studies of MPPG were conducted in vitro, as well as in animals and humans. In vitro experiments showed an antioxidative effect of MPPG on LDL-C [16, 17] and an anticoagulant/antiplatelet effect [18]. Calcium-antagonistic effects of MPPG were found in polymyopathic Syrian hamsters [19] and antiatherosclerotic effects in rabbits and rats [20, 21]. These effects were accompanied by a cholesterol-lowering effect. The mechanism of this effect remains unclear. It cannot be explained on the basis of action of the single constituents magnesium, vitamin B6 or glutamate. None of these shows a cholesterol lowering effect.

Most human studies with MPPG have been unblinded, uncontrolled, non-randomised or unpublished. Nevertheless, the outcome tendency has been that MPPG has a favourable effect on TC, LDL-C, HDL-C and triglycerides. Three carefully designed, double-blind, placebo-controlled, randomised clinical trials have been published [13, 14, 15]. The first was done in patients with renal insufficiency (MPPG/placebo: 15/15), treated with three daily doses (dd) 50 mg MPPG for 12 weeks [13], the second in patients with type-IIb hyperlipidaemia (74/75), treated with 3 dd 150 mg for 6 months [14] and the third in patients with familial hypercholesterolaemia (9/10), treated with either 3 dd 150 mg for 8 weeks or 4 dd 150 mg for eight consecutive weeks [15]. The first two studies demonstrated a considerably favourable effect of MPPG relative to placebo, on TC, LDL-C, HDL-C and triglycerides. These results could not be confirmed by the third study. So far, no effects have been demonstrated on Apo-A1 and Apo-B [14, 15], fibrinogen [14] or lipoprotein (a) (Lp(a), [15]). The authors of this last study [15] could not give an adequate explanation for their divergent results.

On the basis of the pharmacological properties of MPPG, the likely effects of this substance on primary hypercholesterolaemia and mixed dyslipidaemia, the low-risk profile with hardly any side effects and the fact that a cholesterol-lowering drug is primarily a tool in the hands of general practitioners (GPs), we found it worthwhile to investigate the efficacy and effectiveness of MPPG compared with placebo in a GP setting. Efficacy was calculated by comparing differences in mean cholesterol levels after an intervention period of 3 months, whereas a period of 12 months was used to study the clinical effectiveness of MPPG.

**Methods**

Setting and ethical approval

The study was conducted between May 1993 and December 1996 in Mierlo, a village with approximately 10,000 inhabitants, 15 km south-east of Eindhoven (in the southern part of the Netherlands). Prior to the randomised, placebo-controlled, double-blind intervention trial (RCT), the entire adult population of this village entered a selection protocol aimed at detecting subjects with an increased risk of cardiovascular disease. Enrolment in the RCT took place simultaneously with the selection part of the study.

In Mierlo, five GPs collaborate in one health centre, which also houses the local pharmacy. The selection procedure was conducted at one location in the village, separated from the health centre and specially equipped for this purpose. At this selection centre, one experienced practice–research nurse and one previously trained researcher were responsible for the logistics (mailings, making appointments, transportation of blood samples) and the physical examinations (blood pressure, height, weight). They also asked the patients about their physical activities and smoking habits and conducted the blood sampling (also during the RCT). Their training was based on the relevant guidelines of the Dutch College of General Practitioners (NHG) [22, 23].

All five GPs participated in the RCT. Each GP was responsible for those patients who were on his list. One GP was also responsible for a group of patients who were on the list of a GP outside the village or who had no GP at all. The pharmacy’s task was the storage and supply of the trial medication. The samples were analysed at the laboratory of the local hospital in Geldrop. This laboratory is involved in a national quality assurance program. The protocol for the RCT was approved by the medical ethics committee of Maastricht University and the University Hospital Maastricht (the Netherlands).

Subjects, randomisation and power

On the basis of the municipal register, all inhabitants of the village born between 1 January 1928 and 31 December 1968, and, thus, aged 26–66 years at the time of the RCT, were recorded in the database. These subjects were sent a questionnaire by mail.

The questionnaire consisted of six questions regarding the presence or awareness of risk factors for cardiovascular diseases:

1. Do you suffer from a cardiovascular disease?
2. Does your father or mother or any of your brothers or sisters suffer from a cardiovascular disease or a high cholesterol level?
3. Do you suffer from diabetes?
4. Do you suffer from hypertension?
5. Is your weight in kilograms more than your length in centimetres minus 100?
6. Do you smoke more than five cigarettes a day?

If one or more of the questions on the returned questionnaire had been answered by ‘yes’ (or undecided), the subject was invited for a further examination at the selection centre. The examination involved diastolic and systolic blood pressure measurements, in accordance with the NHG Hypertension Guideline [22], at the beginning and at the end of the visit. In between these measurements, their height and weight were measured and standardised questions were asked about physical activity (much, little or no exercise according to the subject’s own opinion) and smoking habits (number of cigarettes per day). A venous blood sample was taken for TC assay. Since the screening procedure involved the total adult population, the subjects’ medication was not taken into account.

Subjects with TC of at least 7.0 mmol/l were invited for a second and a third visit. At the second visit, the above procedure was repeated, except for the height measurement. The third visit was similar to the second. This time, subjects were asked in advance to fast (i.e. no food or drink, except water, tea or coffee without cream or sugar, from 2200 hours the previous evening), since levels of HDL-C, triglycerides, Apo-A1, Apo-B, Lp(a) and fibrinogen were to be assayed. LDL-C values were calculated using the Friedewald formula. If the triglyceride value was above 4.0 mmol/l, no calculation for LDL-C was made.

TC was measured in accordance with the NHG Cholesterol Guideline [23]. Three measurements were made within a 2-week time span. If the mean TC was at least 10.0 mmol/l, the person was advised to consult his GP and was excluded from further selection. No particular advice about eating habits or lifestyle was given during the visits.