Review Article

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Probucol will become a new model for treating cerebral infarction with a high risk of hemorrhage: A narrative review

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Abstract:

Lipid-lowering agents are relevant in stroke prevention. Probucol (PU) is an antioxidative and lipid-lowering drug that has been used to treat atherosclerotic cardiovascular diseases and xanthomas. The drug penetrates the core of low-density lipoprotein cholesterol (LDL-C) particles, enhancing the activity of plasma cholesterol l ester transfer protein (CETP) and strengthening the liver scavenger receptor type I, resulting in reducing LDL-C; by increasing the activity of paraoxonase 1, upregulating the antioxidant function of high-density lipoprotein (HDL), and it decreases the serum HDL-cholesterol (HDL-C) level. This drug has been retired from the Western markets for lowering HDL-C levels and Q-interval prolongation. The latter side effect has been rarely reported and may be transient. Recent clinical evidence supports the effectiveness of PU in preventing cardiovascular events and in reducing mortality, irrespective of the reduction of HDL-C. Based on basic research and clinical studies, it appears that PU might be a valuable alternative when statins are ineffective or contraindicated, in patients at high risk of recurrence of cerebral ischemia and hemorrhage.

Keywords:

Bioavailability, cardiovascular, hemorrhage, probucol, risk, secondary prevention

Introduction

Owing to its anticorrosion properties, probucol (PU), an antioxidative stress drug, was initially used as a food additive. The US Food and Drug Administration approved PU as a lipid-lowering drug in 1977, and a summary table of the literature regarding probucol with suggested subdivisions into use in different pathologies is shown in Table 1. Its chemical structure Figure 1 differs from that of other lipid-lowering drugs such as statins. Unfortunately, it is being phased out of the Western market because it lowers the low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).[1,2]

After more than 20 years of clinical research, it has been discovered that although PU lowers HDL-C levels, it does not worsen atherosclerosis.[3-10] In contrast, probucol had a strong antiatherosclerotic effect. Furthermore, PU has strong antiaging, restenosis prevention, and postoperative angioplasty treatment properties, which have piqued the interest of many clinicians in various professions.[11-16] PU is taken aback by the new appeal of this type of old medicine, which has faded from the Western market. Some heavyweight experts have written papers saying, "It is too early for us to give up!"[2] This review focuses on new clinical evidence and secondary prevention mechanisms for cerebrovascular diseases with a high risk of hemorrhage.

Does Lowering Low-density Lipoprotein Cholesterol Raise the Risk of Bleeding?

Since the PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage (PICASSO)

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Table 1: A summary table of 1,241 CNKI literature regarding probulcol with suggested subdivisions into use in different pathologies (Number of papers) dated 2023-8-27

System of disease	Subdivision of disease
Cardiovascular diseases (451)	Stent stenosis (87), coronary heart disease (42), atherosclerosis (127), acute coronary syndrome (47)
Neurology (291) and psychiatry (38)	Cerebral infarction (92), acute cerebral infarction (43), carotid plaque (57), PAS (28), dementia (30)
Emergency medicine (86)	Oxidative stress (42) acute cerebral infarction (31), acute stroke (6)
Endocrine glands (209) and urology (76)	Diabetes (47), diabetic nephropathy (33), early diabetes (9), contrast-induced nephropathy (4)
Ophthalmology and otorhinolaryngology (18)	Diabetic retinopathy (4), nonproliferative diabetic retinopathy (3), diabetic macular edema (2), human retinal pigment epithelial cells (2), retinal photocoagulation (2)
Digestive system diseases (16)	Nonalcoholic fatty liver disease (3), nonalcoholic liver disease (3), diabetic fatty liver disease (1)
Dermatology and venereal diseases (2)	Yellow tumor (1), dermatitis (1)
Traditional Chinese medicine (10)	Diabetes (2), Si-Miao-Yong-An decoction (4), *Ginkgo biloba* extract (1), cordyceps sinensis (2)

CNKI: China National Knowledge Infrastructure, PAS regimen: Combined with antagonistic platelets, regulating blood lipids, antioxidant

study concerning PU was controlled with aspirin or cilostazol, the risk of bleeding is worth analyzing here, and clinicians have had a concern in the past that patients with low cholesterol have a high risk of a cerebral hemorrhage. PU has the effect of lowering LDL-C. Therefore, this topic is set as a subtitle of this review.

Lipid-lowering therapy should be a part of a comprehensive statin-based treatment for ischemic stroke. If patients have used high doses of statins but their LDL-C still does not meet the target standard, or if low doses of statins cause LDL-C intolerance, other drugs, such as PU, must be combined.

Ezetimibe, ezetimibe (ninth member of the Kexin-like preconverting enzyme subtilisin family), alirocumab injection probucol, and antioxidation lipid-regulating drugs[17] are among the drugs with evidence-based medical evidence. PU combined with statins has been shown to further reduce LDL-C and improve blood lipid regulation.[18] PU, an antioxidant and lipid-lowering medication, has a clear advantage over ezetimibe, a cholesterol-absorption inhibitor.

The etiology and recurrence risk of ischemic stroke differ, as do LDL-C target values. The target value of LDL-C for some ischemic strokes with low and medium risk of recurrence was 2.6 mmol/L; for ischemic stroke with high recurrence, it should be reduced to 1.8 mmol/L. However, a subgroup analysis of PCSK9 inhibitors[18] in the most recent study revealed that LDL-C could still benefit from further reduction to 1.4 mmol/L for unstable stroke.

The SPARCL study[19-21] on secondary cerebrovascular prevention revealed that the risk of bleeding increased as the statin dose increased. Further investigation revealed that the relationship between bleeding risk and statin dose was not clear but was related to blood pressure control and a history of cerebral hemorrhage.

From a clinical point of view, for patients with a previous history of cerebral hemorrhage or those with more microbleeds detected by magnetic resonance imaging (MRI), because of their high risk of bleeding, it is necessary to control blood pressure well when using high-dose statins, weighing other risk factors that may increase the risk of bleeding.

At the same time, it should also be considered that large doses of statins have the benefit of stabilizing plaques and their influence on liver and muscle enzymes, glucose metabolism, and cognition. Therefore, it is necessary to balance the benefits and risks. The combined application of multitarget and multimechanism drugs may reduce the side effects of drugs, such as statins.

Clinically, stroke recurrence is often observed, even if LDL is a desirable target standard. In addition to LDL-C, elevated levels of oxidized low-density lipoprotein (ox-LDL) and Lipoproteins a are associated with the risk of ischemic stroke recurrence. Therefore, it is necessary to evaluate the risk and medication more accurately and determine whether oxLDL levels are well controlled.

Probucol May Benefit Ischemic Patients with a High Risk of Hemorrhage

PU is a cholesterol-lipid transfer protein activator. In addition to decreasing cholesterol levels, it affects endothelial function in various ways. According to studies on Southern East Asian subjects known as the PICASSO study,[21,22] PU is beneficial for cardiovascular diseases (CVDs). PU can, therefore, be beneficial for the ischemic stroke prone to hemorrhage. The PICASSO study enrolled 67 large hospitals in South Korea, Hong Kong, Japan, and the Philippines, and the randomized controlled 2 × 2 order clinical experiment. Patients with ischemic stroke who had previously experienced cerebral hemorrhage or ≥2 microbleeds were included in the study. The patients were randomly assigned as shown in Table 2.

Table 2: Groups of patients and drugs assignments

Group	Definition	Dose and usage	Blindness
A	Cilostazol group	Cilostazol 100 mg b.i.d	Double-blinded
B	Aspirin group	Aspirin 100 mg q.d	Double-blinded
C	Probucol + cilostazol group	Cilostazol 100 mg b.i.d Probucol 250 mg b.i.d	Probucol was not advertised as open; blind prognosis evaluation
D	Probucol + aspirin group	Aspirin 100 mg q.d Probucol 250 mg b.i.d	Probucol was not advertised as open; blind prognosis evaluation

Hong KS, Kim BJ, Lee JY, Kwon SU, PICASSO Investigators. Rationale and design of the PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage (PICASSO) study: A randomized-controlled trial. Int J Stroke 2015;10:1153-8

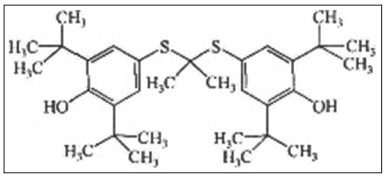

Figure 1: Structure of probucol (4, 4'- [(1-methylethylidene) disulfide] bis [2, 6-Bis (1, 1-dimethylethyl) phenol]). Molecular formula: C31H48O2S2, Molecular weight: 517.86

Blindness: aspirin or cilostazol was intended to be double blinded; PU treatment was not advertised as open but rather as a blind prognosis evaluation.

Main endpoints: the incidence of stroke, myocardial infarction, or vascular death. The incidence of hemorrhagic stroke was the primary composite outcome.

The overall total of 1512 individuals reached the primary complicated objective between August 1, 2009, and August 31, 2015. The ratios and dosages of statins used in the PU and non-PU groups were similar.

The incidence of total vascular events over an average follow-up of 1.9 years (interquartile range, 1.0–3.0) was 4.27 per 100 patients per year in the cilostazol group and 5.33 per 100 patients per year in the aspirin group (hazard ratio [HR]: 0.80, 95% confidence interval [CI]: 0.57–1.11). Comparison of noninferiority, $P = 0.0077$; $P = 0.18$.

Cerebral hemorrhage occurred in 0.61 out of every 100 patients annually and in 1.2 out of every 100 patients annually (HR: 0.51; 97.5% CI: 0.20–1.27; $P = 0.18$).

The results showed that the incidence of compound vascular events and cerebral hemorrhage in the cilostazol group was lower than that in the aspirin group.

The incidence of vascular events was 3.91 per 100 patients per year in the PU group and 5.75 per 100 patients per year in the non-PU group (HR: 0.69, 95% CI: 0.50–0.97).

The incidence of cerebral hemorrhage was 0.72 per 100 patients per year and 1.11 per 100 patients per year, respectively ($P = 0.0316$ for the best effect comparison; HR: 0.65, 97.5% CI: 0.27–1.57; $P = 0.55$).

This result showed that the incidence of compound vascular events and cerebral hemorrhage in the PU group was lower than that in the non-PU group.

Side effects were similar in all four groups. Vertigo, headache, diarrhea, and constipation were the most common side effects. In other words, PU did not increase the rate of side effects.

The results of the PICASSO study suggested cilostazol are not inferior to aspirin in protecting against cardiovascular events in ischemic stroke patients with a high risk of cerebral hemorrhage. The vascular incident occurrence rate decreased when PU was used on the background of aspirin or cilostazol.

Randomized controlled trial (RCT) findings from the PICASSO study are the highest level of evidence-based medicine. According to the findings of the PICASSO study, PU is an optional drug for this conundrum if clinical data indicates a high risk of stroke recurrence and MRI imaging data point to a high risk of a cerebral hemorrhage.

No discernible difference was observed in the safety of PU and the placebo in terms of the risk of cerebral hemorrhage. To meet the clinical practice design, antioxidant regimens were considered in this PICASSO study.

With advances in evidence-based medicine, antioxidant therapy will become one of the three pillars of secondary stroke prevention. Therefore, one alternative for the secondary prevention of stroke is the proper use of PU. If the three cornerstones are unstable, then the better option is PU for ischemic stroke with a high risk of hemorrhages.

Probucol was Abandoned by Western Countries for High-density Lipoprotein Cholesterol Reduction but High-density Lipoprotein Cholesterol Reduction may not be Harmful

Two clinically controlled randomized trials, prospective and impact,[10] were used in the perspective and influential comprehensive analysis of two PUs for

the secondary prevention of cardiovascular events. The trials were to examine the effects of PU on the thickness of carotid intima–media known as IMT and cardiovascular events in patients with CVD in Southeast Asia. 1,025 patients were enrolled in this study. Carotid intima–media thickness (IMT), blood lipid levels, and the onset of the first significant adverse cardiovascular and cerebrovascular events were compared between groups. The findings from the trials showed that reduced HDL-C did not increase adverse events, such as severe ventricular arrhythmia. This result showed that PU had some impact on the secondary prevention of cardiovascular events, the adjusted risk ratio (HR) and 95% CI were 0.67 and 0.44–1.03, respectively. The mean IMT did not increase significantly between the control and PU groups.

The effects of cilostazol and PU on the risk of cardiovascular events were inconsequential, despite a decrease in HDL-C levels. Pharmacologically decreased HDL-C levels may be inaccurate indicators of cardiovascular event risk. When statins are ineffective, PU should be considered because it is effective in lowering the risk of coronary heart disease.[23,24]

PU has many pharmacological properties. Recent research showed that cholesterol ester transfer protein or scavenger receptor type BI-related HDL metabolism is new pharmacological targets at the molecular level. Decreasing HDL-C may not be a "side effect" but is most likely a novel mechanism of PU. There is solid ground for thinking that older medication, such as PU performs better than any currently available modern medication.

In addition to prior studies showing that PU may be beneficial for the prevention of secondary cerebrovascular diseases,[25-27] Hirata[28] listed "New Evidence of PU on Cardiovascular Events" based on the prospective study of 876 Japanese patients with coronary artery diseases and dyslipidemia and the result was positive.

Problems and Perspectives

A major pathogenic factor of atherosclerosis is the local oxidative stress microenvironment. PU has anti-inflammatory, antioxidation, and hypolipidemic effects, showing great potential to treat atherosclerosis. Its low bioavailability limits its wider application. The oral dose of PU 84% is excreted from the stool in the primary form.

PU encapsulated RP-PU with star-shaped polymer and erythrocyte membrane showed lower solution viscosity, smaller hydrodynamic radius, and higher drug loading than linear polymer.[29] RP-PU has a good sustained release effect and excellent biocompatibility. RP-PU can be efficiently internalized by cells to improve biodistribution. The treatment of ApoE-/-mice with RP-PU effectively reduced the blood lipids levels and related metabolic enzymes. Compared with the control group and the PU group, the collagen fibers in the aortic root of the RP-PU group decreased. Moreover, RP-PU reduced the expression of monocyte chemoattractant protein-1 and ICAM-1, inhibited foam cell formation, and delayed atherosclerosis formation. Therefore, RP-PU biomimetic nanoparticles can be used as nanotherapeutic drugs for antiatherosclerosis. Red blood cell biomimetic nanoparticles with anti-inflammatory, antioxidation, and hypolipidemic effects are expected to be used in the clinical treatment of atherosclerosis.

The risk of stent thrombosis in the first few months after the stent implantation is determined by incomplete strut coverage. At 3 months, a novel PU-coated polymer-free ultrathin strut sirolimus-eluting stent[15] demonstrated significantly better early strut coverage.

Large-scale RCT studies showed similar adverse reactions, such as vertigo, headache, diarrhea, and constipation being the most common.[30-32] The latest patented drugs are PU sustained-release capsules, which may reduce gastrointestinal reactions while increasing absorption and utilization.[28,33,34] The PU specification states that a rare adverse reaction in China[35] is Q-T interval prolongation. Merrell Dow[36] has made statistics that there have been 27 cases of prolonged Q-T intervals in 3 million prescriptions, with no serious consequences after drug withdrawal. Pharmaceutical experts believe that macrolide antibiotics also have this problem and the PU problem is much milder; therefore, it is safe. Amiodarone can improve myocardial function by prolonging the QT interval. PU prolongs the Q-T interval, which may be due to intermediate electrophysiological changes. PU is effective in lowering the risk of cardiovascular events and has the potential to reduce cardiac mortality.

An essential line of research in the future would be precisely the assessment of the role of PU for secondary prevention of cerebral infarction with a high risk of a cerebral hemorrhage in lacunar versus nonlacunar ischemic stroke,[37-41] because the pathophysiology, prognosis, and clinical features of lacunar strokes are different from other acute cerebrovascular diseases.

The limitations of this article are that only the evidence of PU and cardiovascular and cerebrovascular diseases is collected, and other pharmacological effects of PU are rarely mentioned. The next step is to analyze the extensive clinical application of PU to fully demonstrate the advantages of PU in antioxidation and lipidlowering.

Conclusion

PU alleviates atherosclerosis, improves HDL function, and does not increase the risk of cardiovascular events. PU-induced pharmacological changes in HDL-C may not be a reliable prognostic marker for cardiovascular risk. Q-T interval prolongation is a rare adverse reaction as described in the manufacturer's instructions, but prolonged Q-T interval may only be an intermediate pharmacological phenomenon of electrophysiological changes. PU is beneficial for secondary prevention of cardiovascular events and reduces mortality without increasing the risk of cardiovascular and cerebrovascular adverse events. PU is not permitted to be used when the electrocardiogram Q-T interval is prolonged, or if there is severe ventricular arrhythmia as described in the instructions. To avoid unnecessary trouble, clinicians should prescribe drugs according to the manufacturer's instructions before the drug instructions are revised.

PU is a safe and well-tolerated drug not been found carcinogenic effects or mutagenic effects. PU will become a useful supplement to the three cornerstones of secondary prevention of ischemic cerebrovascular disease. For patients with cerebral infarction at risk of bleeding, PU will be a hope to solve the dilemma of bleeding and ischemia at the same time due to its unique cholesterol-lowering and antioxidant functions.

Ethical statement
Not applicable.

Data availability statement
The datasets generated during and/or analyzed during the current study are available in the PubMed repository, www.pubmed.org/download/.

Authors' contributions
LLG and ZJY analyzed the data; ZDJ prepared the manuscript, and HMG wrote the article (research literature, design thesis framework, drafting papers, revising papers, and final thesis).

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Conflicts of interest
There are no conflicts of interest.

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