Interaction between policosanol and prostacyclin on platelet aggregation in rats

MARÍA DE LOURDES ARRUZAZABALA, ROSA MÁS, DAISY CARBAJAL, SURIA VALDÉS and VIVIAN MOLINA.

Departamento de Farmacología, Centro de Productos Naturales, Centro Nacional de Investigaciones Científicas, Avenida 25 y 158, Playa, Apartado Postal 6412, Ciudad de La Habana, Cuba.

Palabras clave: policosanol, prostaciclina, interacción, agregación plaquetaria.
Key words: policosanol, prostacyclin, interaction, platelet aggregation.

INTRODUCTION

Policosanol is a mixture of higher molecular aliphatic primary alcohols, isolated from sugar cane wax, (Saccharum officinarum, L.) whose main component is octacosanol. Oral treatment with policosanol reduces serum cholesterol levels in different experimental models, healthy volunteers and patients with type II hiperlipoproteinemia. Previous results showed that policosanol orally administered inhibits platelet aggregation induced in vivo by collagen and induced ex vivo by ADP in rats. It also disaggregates platelets in vitro by ADP in rats as well as significantly reduces serum thromboxane B2 levels in rats, Mongolian gerbils, and mice and increases prostacyclin serum levels in Mongolian gerbils. It has been shown that policosanol also exhibits antiplatelet properties in human beings.

Prostacyclin (PGI2) is the most potent endogenous inhibitor of platelet aggregation discovered so far. It also disaggregates platelets in vitro and can prevent or reverse aggregation.

There are alternative approaches for enhancing the therapeutic action of PGI2. One of them is the concomitant use of a phosphodiesterase in-
The antiaggregatory activity of PgI₂ was assessed by determining the percentage of inhibition on ADP (5 μmol/L)-induced PRP aggregation in the presence of PgI₂ (1 · 10⁻⁸ mol/L) or Tris HCl buffer added to PRP 1 min before ADP in PRP of controls and policosanol pretreated animals.

The disaggregatory activity of PgI₂ was assessed by determining the percentage of disaggregation on ADP (12 μmol/L)-induced PRP irreversible aggregation after the addition of PgI₂ (2 · 10⁻⁴ mol/L).

DISCUSSION

A number of disease states have now been related to an imbalance in the vascular PgI₂ and thromboxane A₂ (TXA₂) system.

Patients with arterial thrombosis, deep vein thrombosis and recurrent venous thrombosis produce more of the proaggregatory compounds: PG endoperoxides and TXA₂ in their platelets. Atherosclerotic rabbits and patients who have survived myocardial infarction produce more TXA₂ than controls and they are also very sensitive to other aggregating agents.

Not only diabetic rats release more TXA₂ than normal rats but also their blood vessels show reduced generation of PgI₂. Blood vessels from diabetic patients show reduced production of PgI₂ and circulating levels of 6 oxo PgF₁α, the metabolite of PgI₂, are reduced in diabetic patients with proliferative retinopathy.

Smooth muscle cells obtained from atherosclerotic lesions and cultured in vitro also produced less PgI₂ than normal vascular smooth muscle.

Increased levels of low density lipoproteins (LDL) has been suggested to be a risk factor associated with ischaemic heart disease, meanwhile an inverse relation is shown regarding high density lipoprotein (HDL) levels. LDL reduces the generation of prostacyclin-like substance from human endothelial cells whereas HDL stimulates PgI₂ synthesis. It is likely that the lipid per-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Aggregation (Buffer)</th>
<th>Inhibition (PgI₂) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>59.5 ± 18.6</td>
<td>38.6 ± 4.0</td>
</tr>
<tr>
<td>Policosanol 20 mg/kg</td>
<td>6</td>
<td>49.1 ± 20.3</td>
<td>23.5 ± 11.0</td>
</tr>
<tr>
<td>Policosanol 200 mg/kg</td>
<td>6</td>
<td>31.2 ± 14.6*</td>
<td>10.6 ± 9.0**</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01. Mann Whitney U test. Comparisons with control group.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Disaggregation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>15.4 ± 11.9</td>
</tr>
<tr>
<td>Policosanol 20 mg/kg</td>
<td>6</td>
<td>58.8 ± 3.8*</td>
</tr>
<tr>
<td>Policosanol 200 mg/kg</td>
<td>6</td>
<td>61.6 ± 15.5*</td>
</tr>
</tbody>
</table>

*p < 0.05 Mann Whitney U test.
oxides found in LDL (and not in HDL) may be responsible for the inhibition of \( \text{PGI}_2 \) synthesis.\(^{29}\)

Blood vessels of the brain of all animals species, including man, generate \( \text{PGI}_2 \).\(^{30,31}\) Several investigators have suggested that \( \text{PGI}_2 \) may be involved in the regulation of blood flow in the brain.\(^{32}\)

These results suggest that prostanoids (\( \text{TXB}_2 \) and \( \text{PGI}_2 \)) have a role in platelet function and are involved in cardiovasular disorders.

This concept has provided the basis for the development of compounds with therapeutic potential in reducing intravascular thrombus formation as: cyclooxygenase inhibitors, thromboxane synthetase inhibitors, thromboxane antagonists and \( \text{PGI}_2 \) analogues.\(^{33}\)

Previous results have shown that single doses of policosanol not only are able to reduce \( \text{TXA}_2 \) and malondialdehyde,\(^{34}\) but also increases \( \text{PGI}_2 \) serum levels in several animal models,\(^{35}\) suggesting an thromboxane synthetase inhibitor like effect.

On the other hand, platelets of hyperlipoproteinemic (HLP) patients exhibit a significantly reduced sensitivity to prostacyclin,\(^{36}\) iloprost and \( \text{PGI}_1. \)\(^{34}\) Thus, considerably higher concentrations of these prostaglandins are required to inhibit platelet function in HLP than in healthy controls.

Oliva et al.\(^{34}\) have shown that the number of prostacyclin binding sites in platelet membranes, prepared from platelet–rich plasma, was significantly reduced in type IIa HLP whereas the \( K_d \) indicating the affinity of the binding sites, remained unchanged.

Jaschonek et al.\(^{35}\) using cholesterol-hemisuccinate-loaded platelets, have shown that incorporation of cholesterol results in a decrease of membrane fluidity and an apparent loss of iloprost binding sites while administration of local anesthetics, leading to increased membrane lipid fluidity, exerted the opposite effect.

It has been argued that if the changes in platelet reactivity, sensitivity to \( \text{PGI}_2 \), and eicosanoids biosynthesis reported in hypercholesterolemia are a direct consequence of elevated plasma lipid levels, then one would expect that cholesterol lowering by dietary means, plasma-pheresis, or lipid-lowering drugs would result in normalization of platelet function.\(^{38}\) In fact, LDL apheresis, fibric acid derivatives, ion exchange resins, probucol, and HMG-CoA reductase inhibitors have all been evaluated for their effects on platelet function. In these studies, except those carried out with simvastatin, despite LDL-C reductions on the order of 10 to 30 %, no change in platelet aggregation\(^{39}\) and platelet sensitivity to iloprost\(^{40}\) could be demonstrated ex vivo.

The results of the present work show that policosanol at the same doses reduces thromboxane and increases \( \text{PGI}_2 \) serum levels, enhances exogenous \( \text{PGI}_2 \) antiaggregatory effect in rats.

The fact that policosanol increases not only \( \text{PGI}_2 \) serum levels but also the sensitivity of exogenous \( \text{PGI}_2 \) suggests that it could act preventing the breakdown of \( \text{PGI}_2 \) to its inactive metabolite (6-oxo \( \text{PGF}_{2\alpha} \)).

Although the exact mechanism of antiplatelet action of policosanol is unknown, these results can explain at least partially the protective effect of policosanol on atherosclerotic lesions in experimental models\(^{39}\) and human beings.\(^{40}\)

**BIBLIOGRAPHY**


8. Soltero I., Fuemmayor I., Colmenare J. Estudio comparativo doble ciego de la eficacía y tolerabilidad del policosanol vs. bezafibrate en pacientes con hiperlipoproteinemia tipo II. Arch. Venezolanos Farmac y Terap, 12, 71, 1993.


ACTIVIDADES CIENTIFICAS
MINISTERIO DE EDUCACION SUPERIOR DE CUBA

V ENCUENTRO IBEROAMERICANO
SOBRE LAS CIENCIAS FARMACÉUTICAS Y ALIMENTARIAS

Instituto de Farmacia y Alimentos, Universidad de La Habana
Del 15 al 17 de octubre del 2002.


MODALIDADES: Conferencias, mesas redondas, talleres y posters. 
CUOTA DE INSCRIPCION: 150.00 USD. Se pagará en el momento de la acreditación en el evento.
SEDE: Palacio de las Convenciones de La Habana
COMITE ORGANIZADOR: Dr. Oscar Ros López.
E-mail: ifal@mail.pco.cu
Fax: (537) 33-6811