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ARTICULO DE REVISION

Policosanol: a potentially beneficial therapeutic option in the management of pre-hypertensive patients or with arterial hypertension

Policosanol: una posible opción terapéutica beneficiosa en el manejo de pacientes pre-hipertensos o con hipertensión arterial

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ABSTRACT

Hypertension is one of the most important factors affecting morbidity and mortality from cardiovascular diseases. The main objective of the treatment of hypertension is not only to control blood pressure levels, but also to reduce cardiovascular risk. To reduce cardiovascular risk, it is essential to apply a comprehensive treatment scheme that includes lifestyle changes, antihypertensive drugs, and also, when required, lipid-lowering, antiplatelet, and hypoglycemic treatment. Policosanol is a mixture of high molecular weight alcohols purified from sugar cane wax with lipid-lowering, antiplatelet and antioxidant effects. The objective of this review is to analyze arterial hypertension and the possible beneficial use of policosanol in the treatment of pre-hypertensive patients or those with arterial hypertension. The proposal for the use of policosanol in reducing blood pressure values is based on the results of an important group of previously conducted clinical studies, in which as part of the safety analysis when evaluating the effect of policosanol on blood pressure values, it was observed that in patients treated with policosanol, there was a significant reduction in these values, similar to the results obtained in another group of clinical studies, which have shown that treatment with policosanol reduces systolic and diastolic blood pressure values, when it is determined by different methods and in distinct treatment periods, both in pre-hypertensive subjects and in hypertensive patients. Meta-analyses of some randomized controlled clinical trials have also shown that policosanol treatment reduces blood pressure values, which is associated not only with its main effects, but also with its beneficial pleiotropic effects on the vascular tree.

Key words: Policosanol, blood pressure, pre-hypertension, hypertension.

RESUMEN

La hipertensión es uno de los factores más importantes que afectan la morbilidad y mortalidad por enfermedades cardiovasculares. El principal objetivo del tratamiento de la hipertensión no es sólo controlar los niveles de presión arterial, sino también reducir el riesgo cardiovascular. Para reducir el riesgo cardiovascular, es imprescindible aplicar un esquema de tratamiento integral que incluya modificaciones en el estilo de vida, fármacos antihipertensivos, y también, cuando se requiera, tratamiento hipolipemiante, antiplaquetario e hipoglucemiante. El policosanol es una mezcla de alcoholes de alto peso molecular purificados a partir de la cera de la caña de azúcar con efectos hipolipemiantes, antiplaquetarios y antioxidantes. El objetivo de esta revisión es analizar la hipertensión arterial y el posible uso beneficioso del policosanol en el tratamiento de pacientes pre-hipertensos o con hipertensión arterial. La propuesta del uso de policosanol en la reducción de los valores de presión arterial se sustenta en los resultados de un importante grupo de estudios clínicos realizados previamente, en los que como parte del análisis de seguridad al evaluar el efecto del policosanol sobre los valores de presión arterial, se observó que en pacientes tratados con policosanol, hubo una reducción significativa de estos valores, al igual que los resultados obtenidos en otro grupo de estudios clínicos, que han demostrado que el tratamiento con policosanol reduce los valores de la presión arterial sistólica y diastólica, cuando ésta se determina por diferentes métodos y en distintos períodos de tratamiento, tanto en sujetos pre-hipertensos como en pacientes hipertensos. Los meta-análisis de algunos estudios clínicos aleatorizados y controlados también han demostrado que el tratamiento con policosanol reduce los valores de presión arterial, lo que no solo se asocia con sus efectos principales, sino también con sus efectos pleiotrópicos beneficiosos sobre el árbol vascular.

Palabras Claves: Policosanol, presión arterial, pre-hipertensión, hipertensión.

INTRODUCTION

Epidemiology and prevalence of hypertension: Hypertension is one of the most important factors that affect morbidity and mortality in patients from cardiovascular diseases. Substantial progress has been made in understanding the epidemiology, pathophysiology, and risk associated with hypertension, and lowering blood pressure has been shown to reduce cardiovascular morbidity and mortality (Ettehad *et al*, 2016; Foruuzanfer *et al*, 2017; NCD Risk Factor Collaboration, 2017).

Different proven and effective therapeutic strategies, as well as through lifestyle changes, blood pressure can be lowered; however, blood pressure control is insufficient and as a consequence, hypertension continues to be the largest preventable cause of cardiovascular disease and all-cause mortality worldwide (Banegas *et al*, 2011; Chow *et al*, 2013).

Hypertension is defined as the elevation of systolic blood pressure (SBP) to 140 mmHg or more, or diastolic blood pressure (DBP) to 90 mmHg or more, or both values inclusive. This definition is applicable to adults (young, middle-aged and elderly adults), since in children other figures or blood pressure values are defined according to their age, sex and height (Whelton *et al*, 2017; Williams *et al*, 2018; Oparil *et al*, 2018).

The hypertension classification for adults 18 years of age or older, which is set out below, is based on the figures or values of blood pressure and has the purpose of identifying individuals at risk of suffering from hypertension (pre-hypertensive), as well as facilitate a Cuban practical guide for the treatment and evolution of the hypertensive patients (Table 1) (Pérez *et al*, 2017).

Table 1. Blood pressure classification based on values for adults 18 years and older.

Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Normal	Less than 120	Less than 80
Pre-hypertension	120-139	80-89
Hypertension Grade I	140-159	90-99
Hypertension Grade II	160-179	100-109
Hypertension Grade III	180 and more	110 and more
Isolated systolic hypertension	140 and more	Less than 90

Hypertension is an important factor that affects mortality from cardiovascular diseases and the continuous relationship between blood pressure values and cardiovascular and renal complications is sufficiently demonstrated, being such a relationship independent of other risk factors, which is true for all ages and all ethnic groups. For individuals between the ages of 40 and 70, every 20 mmHg increase in systolic blood pressure or 10 mmHg in diastolic blood pressure doubles the risk of cardiovascular disease over the entire range from 115/75 to 185/115 mmHg (Whelton *et al*, 2017).

SBP is a more powerful predictor of complications than DBP after 50 years of age and it has been suggested that pulse pressure has an additional prognostic role in the elderly, and indicated by the particularly high cardiovascular risk observed in patients with isolated systolic hypertension. These findings have been proven both when the blood pressure measurement is used in the office, with the self-measurement of blood pressure and by ambulatory blood pressure monitoring (Whelton *et al*, 2017; Williams *et al*, 2018).

It is very common for hypertensive patients to coexist with other coronary risk factors that can modify and increase cardiovascular morbidity and mortality; known as metabolic risk factors, which are more common with high blood pressure than with low blood pressure. In the world, the prevalence of hypertension ranges between 30% and 45% of the general population regardless of the geographical area or economic level of the country (Sur *et al*, 2019).

Hypertension is more common at advanced ages, reaching a prevalence that exceeds 60% of people over 60 years of age and as populations age, adopt a more sedentary lifestyle and increase body weight, the prevalence of hypertension will continue to increase throughout the world, with the number of people with hypertension estimated to increase by 15-20% in 2025, reaching 1,500 million (Forouzanfar *et al*, 2017).

In Cuba, the prevalence of hypertension is 30.9% in people aged 15 or over, which means that there are 2.6 million people with hypertension, slightly higher in urban areas (31.9%) than in rural areas (28%) and without significant differences in sex, with 31.2% male and 30.6% female. There is a higher prevalence in black-skinned people with 40.4% than in white-skinned people with 30.1% (MINSAP, 2020).

As age increases, the prevalence increment, observing that from 55 years of age, 5 to 6 people in 10 have high blood pressure figures and the global prevalence of pre-hypertension is 15.6% with respect to the entire population (Whelton *et al*, 2017; Williams *et al*, 2018).

A strong relationship between the prevalence of hypertension and mortality from stroke and cardiovascular disease has been described. In Cuba, the mortality rate per 100,000 inhabitants from heart disease in 2020 was 218.3 (men: 231.0 and women: 205.6) and 82.6 due to cerebrovascular diseases (men: 82.6 and women: 82.7), figures that show a sustained upward trend in recent years (MINSAP, 2020).

Other risk factors usually coexist in hypertensive patients, which worsens their risk; such as smoking, diabetes mellitus, dyslipidemia, overweight, obesity, the consumption of alcoholic beverages and insufficient physical activity. This overview shows us the characteristics that our hypertensive patients frequently have and that without their modification it would be impossible to reduce their cardiovascular risk (Sur *et al*, 2019).

Hypertension and cardiovascular risk: The relationship between blood pressure and the risk of cardiovascular events is continuous, consistent and independent of other risk factors. The higher the blood pressure, the greater the chance of heart attack and heart failure (Whelton *et al*, 2017).

The need to reduce morbidity and mortality from cardiovascular disease has been the main reason for approaching the problem of hypertension control from a more comprehensive point of view and not only focused on blood pressure figures as the main variable to decide the need and type of treatment. This approach is based especially on the success demonstrated by preventive aspects in reducing mortality from cardiovascular disease in Western European countries, Canada, and the United States (Kjeldsen, 2018).

On the other hand, it is known that only a small fraction of the hypertensive population has only high blood pressure, while the vast majority have additional coronary risk factors. Furthermore, when they coexist, hypertension and other coronary risk factors can be mutually reinforcing, resulting in a greater risk than the sum of their individual components (Naser *et al*, 2016)

In individuals with complications of hypertension, diabetic or not, and with high cardiovascular risk, antihypertensive treatment strategies, as well as other treatments, may be different from those indicated for low-risk individuals. There is evidence that, in high-risk individuals, blood pressure control is more difficult and frequently requires the combination of antihypertensive drugs with other treatments, such as intensive lipid-lowering therapy and antiplatelet therapy (Fuchs & Whelton, 2020).

Atherosclerosis is the physiopathogenic and anatomopathological basis of cardiovascular diseases and is usually the result of a set of risk factors, among which hypertension stands out for its importance (Ettehad *et al*, 2016). Hypertension rarely occurs alone and is often grouped with other cardiovascular risk factors, such as dyslipidemia and glucose intolerance. This grouping of metabolic risk has a multiplier effect on cardiovascular risk, thus, quantifying total cardiovascular risk (that is, the probability that a person will suffer a cardiovascular complication in a given period of time) is an important part of the process of risk stratification of people with hypertension (Berry *et al*, 2012).

The prevention of cardiovascular diseases in hypertensive patients must be adapted to their cardiovascular risk, the higher the risk, the more intensely the strategy to control and reduce it must be applied (Fushs & Whelton, 2020).

Low risk. Hypertensive patient without other additional coronary risk factors and grade I blood pressure; pre-hypertensive patient with ≥ 1 additional risk factor.

Moderate risk. Hypertensive patient without other additional coronary risk factors and grade II blood pressure; patient with ≥ 1 coronary risk factor and grade I or II blood pressure; pre-hypertensive patient with ≥ 3 coronary risk factors or with lesion in the target organ or with diabetes mellitus.

High risk. Patient without other coronary risk factors and grade III blood pressure; patient with ≥ 1 coronary risk factor and grade III blood pressure; and patient with ≥ 3 coronary risk factors or with lesion in the target or diabetic organ, and any degree of blood pressure.

The therapeutic strategy must take into account cardiovascular risk, in addition to blood pressure levels, to maximize the cost-effectiveness ratio in the management of hypertension.

Diagnostic evaluation: The measurement of blood pressure must meet important requirements to do it accurately, since at the starting point of this, the appropriate behaviors will be specified that will be taken individually (Byrd & Brook, 2019).

Therapeutic strategies: There are two widely established strategies for lowering blood pressure: lifestyle interventions and drug therapy, although new device-based therapies are currently emerging but have not yet proven their efficacy as a treatment option.

There is no doubt that lifestyle interventions can reduce blood pressure and, in some cases, cardiovascular risk, but most hypertensive patients require additional drug therapy. This is based on firm evidence, supported by the results of the largest number of randomized clinical trials that have been conducted to date.

Meta-analyzes of randomized clinical trials involving several hundred thousand patients have shown that a reduction of 10 mmHg in SBP or 5 mmHg in DBP is associated with significant reductions in serious cardiovascular complications (~ 20%), all-cause mortality (10-15%), stroke (~ 35%), coronary complications (~ 20%), and heart failure (~ 40%). These relative risk reductions are constant, regardless of baseline blood

pressure values in the hypertension range, cardiovascular risk level, comorbidities (diabetes, chronic kidney disease), age, sex, and ethnic group (Ettehad *et al*, 2016; Brunstrom & Carlberg, 2018).

Another important goal of antihypertensive treatment is to reduce the development of chronic kidney disease; however, the slow decline in kidney function in most hypertensive patients makes it difficult to demonstrate the potential benefits of lowering blood pressure. Therefore, the protective effect of lowering blood pressure for kidney function is less obvious and has been restricted to patients with diabetes or chronic kidney disease, whose disease progresses more rapidly. Some, but not all, angiotensin converting enzyme inhibitors (ACEI) trials have shown a protective effect of lowering blood pressure against the progression of chronic kidney disease to end-stage in diabetic and non-diabetic nephropathy (Ettehad *et al*, 2016; Brunstrom & Carlberg, 2018).

The recommendations that follow are based on the available evidence from randomized clinical trials; however, these studies based on clinical results have limitations, the most important of which are that the data are derived mainly from elderly or high-risk patients, recruited to increase statistical power, and that the follow-up is relatively short and rarely exceeds 5 years. Therefore, recommendations for lifelong treatments for younger or lower-risk patients are necessarily based largely on extrapolation of data. Currently, the large databases of national health systems registries and the long-term follow-up of clinical studies have become an important source of information on the long-term effects of chronic treatment, in addition to the evidence provided by studies observational studies lasting several decades, evidence indicating that the benefit of continuous treatment is maintained for decades (Kjelsen *et al*, 2014).

In the treatment of hypertension, the fundamental premise must be the individualization of the therapy, with two types of treatments: non-pharmacological and pharmacological.

Non-drug treatment or lifestyle modifications: A healthy lifestyle can prevent or delay the onset of hypertension and reduce cardiovascular risk. Effective changes in lifestyle may be sufficient to delay or prevent the need for pharmacological treatment in patients with grade 1 hypertension; they can also enhance the effects of hypotensive treatment, but should never delay the establishment of pharmacological treatment in patients with organic damage caused by hypertension or with a high level of cardiovascular risk. One of the biggest drawbacks of lifestyle modification is poor adherence over time (Piepoli *et al*, 2016; Vanvakis *et al*, 2017).

Recommended measures for lifestyle changes that have been shown to lower blood pressure include restriction of salt intake, moderation in alcohol consumption, heavy consumption of fruits and vegetables, reduction and body weight control and regular physical activity. Additionally, tobacco smoking has an acute and long-lasting vasopressor effect that can increase daytime ambulatory blood pressure, although smoking cessation and other lifestyle measures are also important beyond blood pressure, such as prevention of cardiovascular disease and cancer. Interventions related to modifying lifestyles constitute the central axis of the prevention of hypertension and are an indissoluble part of the comprehensive treatment of the hypertensive patient (Piepoli *et al*, 2016).

Lifestyle changes can safely and effectively delay or prevent hypertension in non-hypertensive people, delay or prevent drug treatment in patients with grade 1 hypertension, and contribute to the reduction of blood pressure in hypertensive patients undergoing treatment. pharmacological, which allows a reduction in the number and dose of antihypertensive drugs. In addition to the effect of controlling blood pressure, lifestyle changes contribute to the control of other coronary risk factors and other chronic conditions (Whelton *et al*, 2017; Williams *et al*, 2018).

Lifestyle modifications are summarized in reducing and controlling body weight, reducing salt intake, exercising regularly, quitting smoking, limiting the intake of alcoholic beverages and other suggestions in the diet such as increasing intake of potassium, calcium, antioxidant nutrients, and non-nutrient antioxidants (Ozemek *et al*, 2017).

Pharmacotherapy: Pharmacological treatment will be indicated according to the blood pressure figures and the initial cardiovascular risk in each patient. To initiate and maintain drug treatment, the patient's age, individual needs and dose, the degree of response to treatment, and diseases or comorbid factors that may influence the response to treatment (alcoholism, chronic obstructive pulmonary disease) must be taken into account, as well as the therapeutic formulations of easy administration and optimal efficacy to guarantee a better adherence to the treatment. The most suitable are those that manage to reduce blood pressure figures during the 24 hours and the ideal is to maintain more than 50% of its maximum effect levels during the day. It is recommended to divide the doses and distribute the drugs at different times of the day (Kitt *et al*, 2019).

The main drugs used in the treatment of hypertension according to multicenter studies that have included thousands of patients with hypertension, the results of which are recorded in the most important meta-analyzes published in the medical literature and which are therefore considered first-line treatment of hypertension are: thiazide diuretics, calcium channel blockers, ACEI, angiotensin II receptor antagonists (ARA II) and β-blockers, therefore, they are adequate and recommended to establish or maintain antihypertensive treatment, in monotherapy or in combination (Kitt *et al*, 2019).

Other drugs such as α-blockers, central sympatholytics, peripheral adrenergic antagonists and direct vasodilators, are considered second or third line in the treatment of hypertension, some of them reserved for very specific situations (Kitt *et al*, 2019).

Choice of antihypertensive drugs: For decades there has been sustainable evidence that pharmacological treatment in hypertension reduces the risk of serious cardiovascular complications such as stroke, myocardial infarction, heart failure and other cardiovascular deaths. Furthermore, it is known that regression of target organ injury and microalbuminuria can be accompanied by a reduction in fatal and non-fatal complications (Whelton *et al*, 2017; Williams *et al*, 2018). As already explained, the main focus in hypertensive patients should be centered on their cardiovascular risk and, in the same way, the therapeutic strategy to be applied (Oullet *et al*, 2019).

In hypertensive patients with high cardiovascular risk, regardless of the blood pressure figures, the evidence supports that blood pressure is a considerable component of cardiovascular risk and therefore the prompt introduction of pharmacological treatment is recommended, at the same time that changes in the blood pressure are implemented healthy lifestyle (Whelton *et al*, 2017; Williams *et al*, 2018).

In patients with moderate-risk grade I or II hypertension, several studies (although scarce) have shown significant reductions in stroke rates, for which reason antihypertensive drug treatment should be considered when blood pressure control is not achieved in several consultations, after a reasonable period of several weeks of implementation of lifestyle changes (6 to 8 weeks) (Kjeldsen *et al*, 2018; Fuchs & Whelton, 2020).

In hypertensive patients with low cardiovascular risk, the implementation of lifestyle changes can be extended to several months (up to 3 months), provided that vigilance can be maintained through periodic consultations and if blood pressure control is not achieved, should consider starting antihypertensive treatment (Kjeldsen *et al*, 2018; Fuchs & Whelton, 2020).

The lack of evidence does not allow recommending the establishment of antihypertensive treatment for young individuals with isolated elevation of blood pressure, but they require close monitoring and recommendations on changes in lifestyle (Whelton *et al*, 2017; Williams et al, 2018).

In the case of pre-hypertension, there is no universal consensus in the scientific community, on the one hand, there is evidence that seems to support the benefits of antihypertensive treatment in these patients in reducing cardiovascular morbidity and mortality, but on the other, a non-negligible number of investigations have lacked adequate designs to validate their results (Luders *et al*, 2008).

In pre-hypertensive patients with diabetes or with target organ damage, multiple investigations have shown that antihypertensive treatment is associated with a reduction in fatal and non-fatal cardiovascular events. There are also indications that, in patients with diabetes mellitus with increased urinary protein excretion, the use of drugs with a direct antiproteinuric effect, such as inhibitors of the renin angiotensin system decrease the deterioration of renal function and improve cardiovascular risk even in patients in whom blood pressure it is not elevated (Nissen *et al*, 2004; Go *et al*, 2014).

In patients with pre-hypertension and low cardiovascular risk, the application of intense measures of lifestyle modification should be recommended, maintaining close monitoring of blood pressure given the relatively high probability of progressing to hypertension and in those with pre-hypertension with moderate cardiovascular risk with target organ damage or diabetes mellitus, the use of antihypertensive drugs can be considered, especially those that have proven efficacy in protecting against target organ damage and in the appearance of proteinuria in diabetes mellitus (Nissen *et al*, 2004; Go *et al*, 2014).

Evaluation of the hypertensive patient: Evaluation of the hypertensive patient should be based on age, severity of hypertension, personal and family history, physical examination, and results of initial examinations.

Classify hypertension according to degree of severity and rule out secondary causes of hypertension. Assess target organ involvement, detect comorbidities and associated coronary risk factors and if there is suspicion of a secondary hypertension, other investigations related to the cause would be carried out.

Treatment of associated risk factors: The main objective of treating hypertension is not only to control blood pressure levels, but also to reduce cardiovascular risk. To reduce cardiovascular risk, it is necessary to apply a comprehensive treatment scheme that includes lifestyle modifications, antihypertensive drugs, and also, when necessary, lipid-lowering, antiplatelet and hypoglycemic treatment.

-Lipid-lowering treatment: The evidence that reducing plasma cholesterol reduces the cardiovascular risk is unequivocal, the higher the risk, the greater the benefit. In hypertensive patients, it is common to find various alterations in lipid metabolism, and in particular atherogenic dyslipidemia, characterized by high triglyceride and LDL-C (low density lipoprotein-cholesterol) levels and low HDL-C (high density lipoprotein-cholesterol) levels, is commonly observed in hypertensive patients with metabolic syndrome and in diabetes mellitus type 2 (Stone *et al*, 2014).

Multiple investigations have shown the usefulness of lipid-lowering treatment, especially with inhibitors of the enzyme HMG-CoA (hidroxymethylglutaryl coenzyne A) reductase (also called statins), due to their pleiotropic

effects and not only due to the decrease in LDL-C, in the primary and secondary prevention of coronary heart disease and cerebrovascular. Since statins are prescribed for long-term administration, special attention should be paid to interactions with other drugs (cyclosporine, macrolides, azole antifungals, anticalcics, protease inhibitors, sildenafil, warfarin, digoxin, nicotinic acid, fibrates, etc.), since many patients receive pharmacological treatment for concomitant diseases during statin treatment (Go *et al*, 2014).

There is sustainable evidence of the benefit of add statin to antihypertensive treatment in patients with high cardiovascular risk, with target organ damage and in diabetics, regardless of serum cholesterol levels. In these patients, the use of statins is recommended, depending on of the clinical context and the tolerability of the patient. When statins are administered, it is recommended to carry out serum determinations of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatine phosphokinase (CK) to identify the number of patients in whom treatment is contraindicated, or to suspend treatment if these parameters rise with their administration (Stone *et al*, 2014; Cushmen *et al*, 2016).

-Antiplatelet treatment: The benefits of antiplatelet treatment in secondary prevention, especially with low-dose aspirin, are known because a significant reduction in all causes of cardiovascular mortality, myocardial infarction and cerebrovascular disease has been found that is much higher than the risk of bleeding. These results have not been systematically verified in primary prevention, where the reduction of cardiovascular complications does not significantly exceed the risk of bleeding, it is recommended to administer aspirin (75 to 125 mg per day) to all patients with high cardiovascular risk (Whelton *et al*, 2017, Williams *et al*, 2018).

Aspirin should only be given when blood pressure is well controlled. It is not recommended to administer aspirin to hypertensive patients with low or moderate cardiovascular risk, in which the absolute benefit and harm are equivalent. The use of clopidogrel (75 mg/day) is recommended in cases of allergy to aspirin and combined with aspirin in acute coronary syndromes for 9 to 12 months and the systematic combination of aspirin and clopidogrel is not recommended in chronic atherosclerotic disease and stable (Whelton *et al*, 2017, Williams *et al*, 2018).

-Hypoglycemic treatment: In both type 1 and type 2 diabetes mellitus, good metabolic control has been shown to prevent microvascular complications and the risk of cardiovascular disease. On the other hand, in patients with glucose intolerance, the progression to diabetes mellitus can be prevented or delayed with lifestyle modifications; therefore, it is essential to achieve good glycemic control in all patients, regardless of the type of diabetes mellitus, in order to which, depending on the type of diabetes mellitus, requires: therapeutic education that includes dietary suggestions, increased physical activity and body weight control, as well as hypoglycemic drug treatment that is achieved with exclusive insulin therapy (in patients with type 1 diabetes mellitus) and with oral normoglycemic and hypoglycemic drugs (in patients with type 2 diabetes mellitus) (American Diabetes Association, 2017).

Special attention should be paid to hypoglycemic episodes in patients receiving treatment with insulin or drugs that stimulate insulin secretion (sulfonylureas, nateglinide, and replaglinide) (American Diabetes Association, 2017).

It is advisable to individualize the glycemic level to be achieved with pharmacological treatment to avoid the risk of hypoglycemia in frail, high-risk patients, particularly elderly patients with cognitive problems and poor self-care capacity, and to propose a stricter control of hyperglycemia in older patients. young people with recent diabetes mellitus, without complications or with minor vascular complications and with a long life expectancy, so it should be considered to achieve goals of HbA1c <7.0%, fasting plasma glucose <6.0 mmol/L (110 mg/dL) and postprandial glucose <7.5 mmol/L (135 mg/dL), while less strict control should be considered in complicated and frail elderly patients (Whelton *et al*, 2017, Williams *et al*, 2018; American Diabetes Association, 2017).

Follow-up strategies: The monitoring of the hypertensive patient should be supported not only by achieving controlled blood pressure figures in consultation, but also by reducing the cardiovascular risk of each patient. This follow-up should be carried out by the doctor and the family nurse in all patients and should be considered where the conditions created exist, refer patients with high cardiovascular risk and target organ damage to specialized consultations, maintaining follow-up by their area of health (Whelton *et al*, 2017, Williams *et al*, 2018).

After the initiation of antihypertensive pharmacological treatment, the patient should be considered at intervals of 2 to 4 weeks to assess the effects of the treatment on blood pressure and possible side effects until achieving controlled blood pressure levels (<140/90 mmHg) in adults under 60 years of age, regardless of their cardiovascular risk; in patients older than 60 years and SBP ≥160 mmHg, it is recommended to reduce it to 140-150 mmHg as long as they are in good physical and mental condition (Whelton *et al*, 2017, Williams *et al*, 2018).

As already explained in hypertensive patients with chronic kidney disease with proteinuria of more than 1 g/day, in diabetics and in patients with chronic kidney failure it should be considered to achieve blood pressure

levels lower than 130/80 mmHg. Once this objective has been achieved, the evaluation of coronary risk factors and asymptomatic organ damage should be considered at least every 2 years in low and moderate cardiovascular risk and in those with high cardiovascular risk annually (Williams *et al*, 2018).
Once controlled, the finding of elevated blood pressure should always prompt the doctor to investigate the causes, particularly the most common ones, such as lack of adherence to the treatment regimen, persistence of the white coat effect, and occasional or regular consumption of drugs and substances that raise blood pressure or counteract the effects of antihypertensive treatment. This situation requires that the patient (and their family members) be questioned and blood pressure measurements repeated to attenuate the initial alert response, if treatment is considered ineffective for adequate blood pressure control, the regimen of treatment should be modified without delay to avoid clinical inertia (Rapsomaniki *et al*, 2014).

Policosanol

Experimental evidence: Policosanol, a mixture of 8 high molecular weight primary aliphatic alcohols (1-tetracosanol, 1-hexacosanol, 1-heptacosanol, 1-octacosanol, 1-nonacosanol, 1-triacontanol, 1-dotriacontanol, 1-tetratriacontanol) purified from cane wax (Mas, 2000), inhibits cholesterol synthesis (Menéndez *et al*, 1994, Menéndez *et al*, 1996; Menéndez *et al*, 2001) by regulating the activity of HMGCoA (hydroxymethyl glutaryl coenzyme A) reductase, a key enzyme in the synthesis of cholesterol (Singh *et al*, 2006), by activation of AMP kinase (Oliaro *et al*, 2009; Banerjee & Porter, 2010) due to an increase in the production of phosphorylated CaMKK, an effect that requires the metabolism of alcohols into their corresponding acids through peroxisomal β-oxidation (Menéndez *et al*, 2005), data consistent with our results of the metabolism of octacosanol (Menéndez *et al*, 1997). In addition, policosanol increases the number of receptors and the catabolic rate of LDL (low density lipoprotein), which contributes to its ability to reduce LDL-C (low density lipoprotein-cholesterol) levels. The lipid-lowering effects of policosanol persist during long-term therapy (Ng *et al*, 2005; Setnikar *et al*, 2005; Mesa *et al*, 1994; Rodríguez *et al*, 1994).
Policosanol has pleiotropic effects: a) antiplatelet action accompanied by a reduction in plasma levels of thromboxane A_2 (TxA_2) and an increase in prostacyclin (PGI_2) (Arruzazabala *et al*, 1992a; Arruzazabala *et al*, 1992b, Arruzazabala *et al*, 1993), b) antioxidant effects in vivo (Menéndez *et al*, 1999; Ohta *et al*, 2008); c) improvement of the composition and stability of the atherosclerotic plaque (Noa *et al*, 2005), d) anti-proliferative (Noa *et al*, 1999; Noa *et al*, 2001) and e) reduction of circulating endothelial cells in plasma (Noa *et al*, 1997).
Policosanol has prevented the development of induced and spontaneous atherosclerotic lesions in rodents, rabbits, and monkeys (Noa *et al*, 1995, Noa *et al*, 1996; Arruzazabala *et al*, 2000), as well as symptomatology and mortality in induced cerebral ischemia in Mongolian gerbils (Carbajal *et al*, 1994; Arruzazabala *et al*, 1993).
On the other hand, hexacosanol, one of the three most abundant alcohols in policosanol, shows important neuroprotective effects, since it promotes the survival of cholinergic neurons in the septum after experimental axotomy and prevents the degeneration and death of hippocampal neurons induced by intracerebroventricular infusion of kainic acid in rats (Borg *et al*, 1987, Borg *et al*, 1991).
Another study supports the protective effects of octacosanol on 6-hydroxydopamine-induced parkinsonism in rats by preventing the reduction of the levels of pro-neuronal growth factor (pro NGF) and its receptors Taka and p-Akt that mediate the striatum cell survival. Policosanol blocks the expression of the complex (proNGF-p75NTR-sortilin) and preserves the free radical scavenging capacity of the striatum (Wang *et al*, 2010). These data support that, in addition to its beneficial effects on vascular function, policosanol has neuroprotective effects mediated by other mechanisms that contribute to post-stroke neurological recovery.
A study investigating the effect of policosanol on blood pressure and its interaction with propranolol and nifedipine in rats showed that pretreatment with high-dose policosanol (200 mg/day) significantly increased the hypotensive effects induced by propranolol, whereas the effects of nifedipine were unchanged. These results show that policosanol does not antagonize the hypotensive effect of beta-blockers but can increase their hypotensive effect without modifying heart rate (Molina *et al*, 1998).

Clinical evidence

Lipid-lowering effects: Short-term randomized, double-blind, comparative, and open-label studies have shown the lipid-lowering effects of policosanol in normocholesterolemic subjects, patients with type II hypercholesterolemia, postmenopausal women, with multiple risk factors, the elderly, in patients with hypercholesterolemia and liver dysfunction, and in type diabetics 2 (Aneiros *et al*, 1993; Aneiros *et al* 1995; Soltero *et al*, 1993a, Soltero *et al,* 1993b; Pons *et al*, 1994; Torres *et al*, 1995; Campilongo *et al*, 1996; Zardoya *et al*, 1996; Benítez *et al*, 1997; Ortensi, *et al*, 1997; Crespo *et al*, 1997; Crespo *et al*, 1999; Prat *et al*, 1999; Alcocer *et al*, 1999; Mas *et al*, 1999; Castaño *et al*, 1999; Castaño *et al*, 2000a, Castaño *et al*, 2000b; Castaño *et al*, 2001; Castaño *et al*, 2002a, Castaño *et al*, 2002b; Castaño *et al*, 2003; Nikitin *et al*, 2000; Menéndez *et al*, 2000;

Fernández *et al*, 2001; Figuera *et al*, 2001; Mirkin *et al*, 2001; Pella *et al*, 2002; Wright *et al*, 2004; Chen *et al*, 2005; Wang *et al*, 2008; Musto *et al*, 2010).

Long-term studies have demonstrated the persistence of these effects (Pons *et al*, 1994; Canetti *et al*, 1995a, Canetti *et al*, 1995b; Canetti *et al*, 1997, Mas *et al*, 2001; Castaño *et al*, 1995; Castaño *et al*, 2002; Castaño *et al*, 2004) and short-term studies have investigated the effects of policosanol + statins, fibrates or Omega-3 fatty acids therapies (Castaño *et al*, 1998, Castaño *et al*, 2005; Marcello *et al*, 2000).

Policosanol (5-20 mg/d) reduces serum LDL-C and total cholesterol in a dose-dependent manner, reaching the maximum effect at 20 mg/d. Short-term LDL-C reductions have ranged between 13.4% and 17.7% (5 mg/d), between 20.2% and 23.2% (10 mg/d), and between 26.1% and 37.8% (20 mg/d). Doses of 5, 10 and 20 mg/day have achieved increases in HDL-C of 9.0%, 28.9% and 36.4%, respectively, while their effects on triglycerides are modest. The effects appear after 8-12 weeks of therapy and its withdrawal does not cause a rebound effect.

Short-term comparative studies have shown comparable reductions in LDL-C with policosanol 10 mg/d, lovastatin 20 mg/d, simvastatin 10 mg/d, pravastatin 10 mg/d, fluvastatin 20 mg/d, and lower than atorvastatin 10 mg/d. The effects on HDL-C have generally been better than those of statins. On the other hand, policosanol (10 mg/d) produced greater reductions in LDL-C and total cholesterol and increases in HDL-C than bezafibrate and gemfibrozil, although these were more effective in reducing triglycerides.

The lipid-lowering efficacy of policosanol is not only maintained, but is enhanced in the long term. Thus, while doses of 5 mg/d for 1 year reduced LDL-C figures by 23.7%, 10 mg/d produced greater reductions (24.8% - 27.5%).

A meta-analysis of policosanol studies (4596 patients) found that the mean LDL-C reduction (23.7%) with policosanol (5-40 mg/d, 1528 patients) (29 studies) was greater than that achieved with placebo (0.11%) (1406 patients) and with phytosterols and stanols (11.0%) (2-9 g/d) (23 studies) (893 cases) ($p < 0.0001$), concluding that policosanol produced greater reductions in LDL-C and better lipid profile changes.

Antiplatelet effects: Studies in healthy volunteers, patients with type II hypercholesterolemia and type 2 diabetics have demonstrated the antiplatelet effects of policosanol administered at effective doses as lipid-lowering (10 and 20 mg/d) (Valdés *et al*, 1996; Scazziota *et al*, 1996; Arruzazabala *et al*, 1996, Arruzazabala *et al*, 1997; Arruzazabala *et al*, 1998; Arruzazabala *et al*, 2002; Castaño *et al*, 2006; Carbajal *et al*, 1998). Single doses (10-50 mg/d) inhibited significantly and modestly (<20%) platelet aggregation to epinephrine and ADP, while 20 mg/d administered during the half-life of platelets (7 days) produced greater reductions in aggregation by epinephrine (22.5%) and ADP (21%), and modestly inhibited collagen aggregation (11.6%) in healthy volunteers. A lower dose (10 mg/d) administered longer (14 days) inhibited aggregation to arachidonic acid (AA) (25.6%-25.8%), and produced modest reductions in aggregation to epinephrine (17.8%) and collagen (10.1%-16.0%). Increasing doses (10, 20 and 40 mg/d) in successive periods of seven days reduced the aggregation to epinephrine and ADP by 34.7% and 27.8%, respectively, and modestly the aggregation to collagen (13.6%), while 20 and 40 mg/day for 30 days produced similar reductions in aggregation to AA (28.2% and 24.9%, respectively), collagen (21.1% and 20.2%) and ADP (30.9% and 29.1%), so that 20 mg/d produces the maximum antiplatelet effect.

Policosanol (20 mg/d) for 7 days was more effective in inhibiting aggregation to epinephrine (32.6%) and ADP (37.3%) than aspirin (100 mg/d), while aspirin more inhibited aggregation to collagen (61.4%), inhibited the aggregation to epinephrine (21.9%) and did not affect the one induced by ADP. The combined therapy showed advantages, since it markedly inhibited the aggregation to collagen (71.3%), epinephrine (57.5%) and ADP (31.0%). Studies in patients with Type II hypercholesterolemia and type 2 diabetics showed consistent results (Castaño *et al*, 2003; Arruzazabala *et al*, 1998, Arruzazabala *et al*, 2002). Treatment with policosanol + Omega 3-fatty acids revealed a greater antiplatelet effect than Omega 3 + placebo (Castaño *et al*, 2006). The antiplatelet effects of policosanol are accompanied by a reduction in the serum TxA_2 levels and a tendency to increase those of PGI_2.

Antioxidant effects: Some studies have shown the effect of policosanol on LDL oxidation. Doses of 5 and 10 mg/d administered 8 weeks increased the latency (lag phase) (13.0% and 57.0%, respectively) and reduced the maximum oxidation rate (Vmax) (11.4% and 37.7%) of LDL, and the generation of malondialdehyde (MDA) in macrophages (12.4% and 32.2%) (Menéndez *et al*, 2000). Doses of 5 mg/d administered 12 weeks increased the lag phase (14.1%) without modifying the Vmax, and 10 mg/day for 8 weeks increased the phase lag (36.5%) and reduced LDL oxidation Vmax (15.5%), variables not modified by fluvastatin 20 mg/d in patients with type II hypercholesterolemia. Policosanol (10 mg/d) and lovastatin (20 mg / d) administered 8 weeks reduced the Vmax (41.9% and 41.6%) of LDL oxidation in diabetics, but only policosanol increased the lag phase (20.9%) and the total antioxidant capacity of plasma (24.2%) (Castaño *et al*, 2002).

Other effects

Effects in patients with peripheral arterial disease: Policosanol (10 and 20 mg/d for 10-24 weeks) increased the initial (IDC) and absolute (ADC) distance of claudication in patients with intermittent claudication. The effects were marked (≥ 50%) with 20 mg/d, modest-moderate (> 10%, <50%) with 10 mg/d, and persistent after long-term therapy. In addition, policosanol significantly improved lower limb symptoms (pain, coldness, paraesthesia) and the ankle/arm systolic pressure index (SPI), a better marker of peripheral atherosclerosis (Castaño *et al*, 1999; Castaño *et al*, 2001; Castaño *et al*, 2003a, Castaño *et al*, 2003b, Illnait *et al*, 2008). Policosanol 10 mg/d and lovastatin 20 mg/d administered 20 weeks reduced LDL-C in claudicant patients, but only policosanol improved IDC, ADC, SPI and areas of quality of life (perception of health, impact on daily activities), which indicates that they are its pleiotropic effects, not the lowering of LDL-C, which support such improvements (Castaño *et al*, 2003).

Effects in middle-aged subjects: A 5-year cohort study (6611 patients: 3002 controls, 3609 treated) showed a lower frequency of hospitalizations for all causes in the policosanol group than in the control (Mas *et al*, 1999).

Effects in patients with coronary disease: Policosanol (10 mg/d) administered long-term (20 months), in addition to producing cholesterol-lowering effects, produced an improvement in functional and ischemic areas in patients with coronary artery disease (Batista *et al*, 1996), and reduced the frequency of restenosis in obese patients subjected to coronary revascularization (Moreno *et al*, 2005).

Effects in populations with multiple risk factors: Policosanol has reduced the frequency of severe vascular adverse events vs placebo in several studies in these populations.

Effects in the elderly with risk factors: Doses of 5 and 10 mg/d administered 24 weeks increased the ability to perform activities of increasing complexity without feeling fatigue, dyspnea, tachycardia, sweating and / or chest pain.

A study in 1470 elderly people showed that policosanol (5-10 mg/d) administered for three years reduced the frequency of severe adverse events, vascular, coronary, cerebrovascular and total mortality vs placebo (Mas *et al*, 2002).

Effects in patients with carotid stenosis and in patients with ischemic stroke: One study showed that policosanol reduced the progression of carotid lesions vs placebo (Batista *et al*, 1995). On the other hand, 2 open studies in patients with ischemic stroke showed that policosanol (20 mg/d for 5 years), in addition to reducing total cholesterol, improved post-stroke recovery evaluated with the Canadian Scale, none died and only one had recurrent stroke (Ortega *et al*, 2006; Sánchez *et al*, 2010). Two randomized, double-blind studies demonstrated that patients with ischemic stroke treated with policosanol (20 mg/d) + aspirin (125 mg/day) during 6 months they had better neurological recovery, evaluated with the modified Rankin Scale, reduction of platelet aggregation, MDA and LDL-C than with placebo + aspirin (125 mg/d) (Sánchez *et al*, 2012; Sánchez *et al*, 2013), while a comparative study with atorvastatin of three months of treatment showed similar efficacy in terms of the neurological recovery of the included patients (Sánchez *et al*, 2016).

Finally, two long-term studies (12 months) confirmed the effects of policosanol treatment on post-stroke neurological recovery and the benefits on the lipid profile of these patients (Sánchez *et al*, 2017, González *et al*, 2018).

Effects on blood pressure values: Clinical studies carried out in the short (6-12 weeks), medium (6 months) and long term (12-36 months) in patients with type II hypercholesterolemia, postmenopausal women, with multiple risk factors, the elderly, in type 2 diabetics and in patients with ischemic stroke, in which as part of the analysis of safety when evaluating the effect of policosanol on blood pressure values, it was observed that in patients treated with policosanol at its different approved doses there was a significant reduction in systolic and diastolic blood pressure figures, when these were compared with the values baseline, as well as when compared with the control group (placebo, statins or fibrates) (Ortensi *et al*, 1997; Castaño *et al*, 1998; Castaño *et al*, 1999; Castaño *et al*, 2000; Castaño *et al*, 2002; Fernández *et al*, 2001; Mas *et al*, 2001; Más *et al*, 2002; Batista *et al*, 1995; Ortega *et al*, 2006; Sánchez *et al*, 2010; Sánchez *et al*, 2012; Sánchez *et al*, 2013; Sánchez *et al*, 2017).

On the other hand, other clinical studies carried out have shown that treatment with policosanol reduces the values of systolic and diastolic blood pressure, when this is determined by different methods and at distinct treatment periods, both in pre-hypertensive subjects and in hypertensive patients (Kim *et al*, 2017; Kim *et al*, 2018; Cho *et al*, 2018), while a meta-analysis of several randomized and controlled clinical studies showed that treatment with policosanol significantly reduces the values of systolic and diastolic blood pressure (Askarpour *et al*, 2019).

Safety and tolerability: Single dose toxicity of policosanol is practically nil. Sub-chronic and chronic toxicity studies (rats, monkeys, dogs) did not reveal toxicity even at a dose 1724 times greater than the maximum therapeutic. Policosanol showed no evidence of genotoxicity (Ames tests, sister chromatid exchange, bone marrow micronuclei, and mouse spermatogenesis), fetal or reproductive toxicity, or long-term carcinogenic

effects (Gámez *et al*, 2001; Alemán *et al*, 1994a; Alemán *et al*, 1994b; Alemán *et al*, 1995; Fernández *et al*, 2006a, Fernández *et al*, 2006b; Rodríguez *et al*, 1994; Rodríguez *et al*, 1997).

Such results are consistent with clinical studies that have revealed an excellent short and long-term safety profile of policosanol, even in vulnerable populations such as the elderly, patients with liver dysfunction and diabetics. It has not produced effects on the parameters of the physical examination or the laboratory investigated attributable to the treatment. Adverse events have not revealed significant differences vs placebo.

A 4-year pharmacological surveillance study in 27,874 patients confirmed the safety of policosanol, showing a cumulative frequency of adverse events of only 0.3% (Fernández *et al*, 1998). A post-marketing study in the elderly followed for 3 years confirmed the excellent tolerability of the treatment (Fernández *et al*, 2004). The most common adverse events (≤0.05%) reported in post-marketing surveillance studies have been weight loss (0.25%), polyuria (0.13%), polyphagia (0.08%), headache (0.07%), dizziness (0.06%), arthralgia (0.05%) and insomnia (0.05%). As can be seen, none classifies as frequent (≤1%).

The proposal for the use of policosanol in the reduction of blood pressure values is supported by the results of an important group of clinical studies previously carried out, in which as part of the safety analysis when evaluating the effect of policosanol on blood pressure values, it was observed that in patients treated with policosanol at its different approved doses there was a significant reduction in systolic and diastolic blood pressure figures, when these were compared with the baseline values and when compared with the control group (placebo, statins or fibrates), as well as the results obtained in another group of clinical studies carried out, which have shown that treatment with policosanol reduces the values of systolic and diastolic blood pressure, when this is determined by different methods and at different treatment periods, both in pre-hypertensive subjects and in hypertensive patients.

Meta-analysis of several randomized and controlled clinical studies have also shown that policosanol treatment reduces systolic and diastolic blood pressure values, which is not only associated with its main effects, but also with its beneficial pleiotropic effects on the vascular tree. However, to date no study has been conducted specifically aimed at demonstrating such an effect with policosanol on blood pressure in patients with pre-hypertension or grade I hypertension.

We must bear in mind that it is necessary to have drugs that not only act on blood pressure values but also on other factors that favor atherosclerosis, especially in those patients who due to the clinical/diagnostic absence of target organ disease and risk cardiovascular disease, who also have no adherence to changes in lifestyle.

CONCLUSIONS

Policosanol is a potentially beneficial therapeutic option in the management of pre-hypertensive patients or with arterial hypertension. It is necessary to carry out specific clinical studies in this population to confirm this hypothesis.

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