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Review

Antiplatelet activity of drugs used in hypertension, dyslipidemia and diabetes: Additional benefit in cardiovascular diseases prevention

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ABSTRACT

Beyond its function in hemostasis, platelets activation has an important role in cardiovascular diseases (CVD) development. There are different clinical conditions that can mediate abnormal platelet activation and favors pathological thrombosis and CVD. These include Hypertension, diabetes and dyslipidemia, all risks factors from CVD development. Different drugs employed in the handled of these conditions have showed decreases platelet activation and related markers. This effect is in part by improved the base condition; however someone of these drugs can modulate platelet targets. We discuss about underlying mechanisms and the possible implications in the treatment of CVD.

1. Introduction

Cardiovascular diseases (CVD) are the first cause of death in the world and strategies focuses in its prevention have been assembled, which includes changes in lifestyle and drug treatment. Due to the role of platelets in thrombosis development [1], they are frequent therapeutic target in the prevention of CVD [2]. Hypertension, diabetes and dyslipidemia are risk factors for the development of CVD [3] and pharmacological treatment focused on combating these factors is a spearhead in prevention schemes. Furthermore, in these conditions there is a state of platelet hyper-activation and a decrease in the effectiveness of antithrombotic therapy [1,4,5]. Different drugs used in the treatment of these risk factors have been shown decrease platelet activation and prevent the development of CVD. This effect could be due to an improvement in the base condition. However some of these drugs have been shown directly modulate platelet at clinically significant concentrations, which means an additional protective role against developing CVD. We review the antiplatelet effects of different drugs used in prevention of CVD focusing in hypertension, diabetes and dyslipidemia management, that involve a disorder in hemostasis and possible mechanisms behind these effects.

2. Management of cardiovascular disease

Because cardiovascular diseases are the first leading cause of death and disability in the world, health systems have developed strategies to decrease their prevalence in the population. Strategy focuses on general population aims reduce CVD in broad-spectrum population through lifestyle and environmental changes [6]. High-risk approach focused on management of people with high risk factors. Two levels are distinguished, those people who have high risk of developing a first cardiovascular event (*i.e.* primary prevention), or those with established CVD and high risk factor prevalence (*i.e.* secondary prevention) [6]. High risk approaches, in addition to considering the early detection of the population at risk and changes in lifestyle, generally include pharmacological treatment. Hypertension, dyslipidemia, hyperglycemia and diabetes are individual risk factors for the development of CVD. A common approach is to directly attack these factors with lifestyle changes [7–9] or by using pharmacological therapy [10,11].

3. Drugs used in prevention of cardiovascular diseases

Pharmacological treatment is pivotal on CVD prevention and it target specific state or risk factors.

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Table 1
Drugs with antiplatelet activity.

Use	Type	Drug	Model	Dossases	Duration	Effects	Ref
Hypertension	AT_1 receptor blockers	Losartan	Human	50 mg/day	4 weeks	Significantly reduced P-selectin platelets expression	[47]
			Human platelets *in vitro*	10 μM		Reduced TxA2-R agonist induced aggregation	[114]
		Irbesartan	Human platelets *in vitro*	1 and 10 μM		Reduced TxA2-R agonist induced aggregation	[51]
			Hamsters	10 mg/kg	16 weeks	Decreases P-selectin expression and modulate PI3K/Akt signaling	[46]
	Calcium channel blockers	Nifedipine	Human	30–60 mg/day		Reduced adrenaline- and collagen-stimulated aggregation	[53]
			Human platelets *in vitro*	1, 5 μM		Increased the activity and intracellular expression of PPAR-β/-γ	[54]
		Amlopidine	Human	5–10 mg/day	24-Month	Reduced platelet volume, P-selectin exp. and sPselec and beta tromboglobulina (β-TG) levels	[57]
	NHE-1 inhibitors	Cariporide	Human platelets *in vitro*	2 μg/ml		At low pH inhibited ADP induces P-selectin, PAC-1 union and platelet-leucocyte aggregates	[66]
		Eniporide	Human	2.5 and 100 mg (i)		Inhibited NHE-1-mediated platelet swelling	[62]
		Zoniporide	Rabbits	0.25–4 mg/kg/h		Inhibited NHE-1-mediated platelet swelling	[63]
	β-Blockers	Pindolol	Human	5 mg/day	2 weeks	Threshold values of ADP and adrenaline for irreversible aggregation were higher than for propranolol. Increases plasmatic cAMP levels.	[67]
		Propranolol	Human	640 mg/day		Inhibited platelets thromboxane synthesis and platelet aggregation induced by thrombin or arachidonic acid.	[115]
			Human platelets *in vitro*	10–100 μM		Inhibited TxB2 production induced by collagen, preserve cAMP levels at basal and forskolin stimulated, but no for PGE1	[45]
		Metoprolol	Human	100 mg/day	2 weeks	Threshold values of ADP and adrenaline for irreversible aggregation were higher than for propranolol.	[79]
Dyslipidemies	Statins	Simbastatin	Human	20 mg/day	24 weeks	Decrease of platelet-derived microparticles, P-selectins and plasmatic P-selectin levels.	[67]
			Human platelets *in vitro*	20–50 μM		Decrease Ca2, TxA2 formation, PLCγ2 and PKC activation, increases NO, cAMP y cGMP levels and VASP activation	[76]
		Atorvastatina	Human	10 mg/day	3 days	Decrease platelet CD40L and plasmatic sCD40L	[72]
			Human	10 mg/day	4 weeks	Decrease platelet P-selectin	[71]
	Fibrates	Gemfibrozil	Human platelets *in vitro*, enzymatic activity	10-200 μM		sGC NO independent activator, inhibited platelet aggregation, VASP activation.	[79]
Diabetes	Biguanidine	Metformin	Human	850–2550 mg/day	12 weeks	Decrease 11-dehydro-thromboxane B(2) increase antioxidant levels	[88]
	Sulfonylurea	Glimepiride	Human platelets *in vitro*	7.5–480 μM		ADP-induced platelet aggregation inhibitor IC25 15.9 μM	[92]
			Human platelets *in vitro*	20–40 μM		Decrease Ca^{2+} releases induced by thrombin, inhibited the cyclooxygenase pathway	[94]
		Gliclazide	Human platelets *in vitro*	7.5–480 μM		ADP-induced platelet aggregation inhibitor IC25 18.6 μM	[92]
		Gliquidone	Human platelets *in vitro*	7.5–480 μM		ADP-induced platelet aggregation inhibitor IC25 20.4 μM	[92]
		Glibenclamide	Human platelets *in vitro*	20–40 μM		Inhibited (Ca2 +)i elevation induced by thrombin, cyclooxygenase and 12-lipoxygenase pathways	[94]
			Human platelets *in vitro*	1.56–25 μM		Inhibited (Ca2 +)i elevation induced by arachidonic acid	[93]
			Human platelets *in vitro*	1–10 μM		Inhibited aggregation induced by the TPR agonist	[96]
	Thiazolidinediones	Pioglitazone	Human	15–45 mg/day	24 weeks	Decreases PAC-1, p-selectin ADP induces activation	[99]
		Glipizide	Human	5–10 mg/day	24 weeks	Decreases PAC-1, p-selectin ADP induces activation	[99]
		Rosiglitazone	Human	4–8 mg/day	12 weeks	Decreases p-selectin in patients without DMT2	[100]

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