Iptakalim: The new hope on the horizon

Sir,

The multifactorial nature of hypertension evades effective and adequate treatment and there is an ever growing need for drugs targeting different levels in the axis of hypertension. Combination therapy has become the mainstay in management, especially of difficult-to-control hypertension. Many groups of novel antihypertensives have been showing promise and Iptakalim (IPT) is one of them.

The ATP-sensitive potassium channel (KATP) consists of inward rectifier potassium channel subunits (Kir6s) and regulative sulfonylurea receptors (SURs). IPT [2,3-dimethyl-N-(1-methylethyl)-2-butanamine hydrochloride] is a potassium channel opener (KCO) that shows high selectivity to cardiac KATP (SUR2A/Kir6.2) and vascular KATP (SUR2B/Kir6.1 or SUR2B/Kir6.2). IPT protects endothelial cells by activating KATP through preferential activation of the SUR2B/Kir6.1 subtypes of KATP expressed in endothelium, without activation of those in the other tissues. The high selectivity to these channels minimizes the adverse side effects associated with older nonspecific K^+ channel openers. This leads to potassium efflux, which facilitates Ca^{2+} influx resulting in direct activation of endothelial Nitric Oxide Synthase (eNOS) via the classical Ca^{2+}–Calmodulin pathway. The eNOS catalyzes the synthesis of NO in the endothelium, which is crucial in maintaining BP homeostasis and vascular integrity. IPT increases the eNOS expression in cardiac tissue. IPT has shown to restore the imbalance between the NO and endothelial signaling systems during endothelial dysfunction by augmenting the release of NO and inhibiting the endothelin-1 (ET-1) system, resulting in endothelial protection. It protects against the cytotoxicity of Mitochondrial Processing Peptidase (MPP+) and H_2O_2-induced oxidative injury that mediate cardiac injury/hypertrophy by activating mitochondrial KATP channels.[1] IPT results in arteriolar and small artery vasodilation with no or minimal effect on capacitance vessels or large arteries. It also does not have any effect on normotensives and sports a favorable safety and tolerability profile.[2] IPT has no effect on Renin Angiotensin System (RAS), which makes it a valuable alternative when RAS inhibitors are either contraindicated or when combination therapy with any other class of antihypertensives is needed.

IPT offers cardiac antihypertrophic properties (prevents and reverses cardiac and vascular remodeling), helps maintain hemodynamic homeostasis and prevents the progression of cardiac hypertrophy to failure induced by a pressure overload.

It is also shown that IPT remarkably inhibits the levels of Vascular Endothelial Growth Factor (VEGF) mRNA and protein expression and endothelin-1[3] mediated proliferation of pulmonary artery smooth muscle cells which makes it a promising drug in the management of hypoxic pulmonary hypertension. IPT inhibits astrocyte activation and subsequent release of pro-inflammatory factors, thereby protecting the dopaminergic neurons against MPP+ induced degeneration.[4] IPT showed benefit in acute hypobaric hypoxia-induced brain injury (probably via decreased glutamate receptor 1α expression and enhanced glutamate transporter 1 expression) and opens new avenues in stroke management. IPT also showed potential as a new therapeutic strategy in treating type 2 diabetes as experimental studies demonstrated that it closes pancreatic β-cell KATP channels and augments insulin release apart from the additional benefit of alleviating vascular disorders that are rife in diabetes.[5]

Although further large randomized control studies are required to establish its efficacy, IPT certainly holds promise.

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