Phosphodiesterase 5 Inhibition to Treat Essential Hypertension
Is This the Beginning of the Story?

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Treatment of hypertension is a challenging task in cardiovascular medicine. The obviously simple concept that blood pressure (BP) must be “normalized” faces the intrinsic difficulty to decrease BP values, because the effectiveness of available drug classes in terms of BP reduction is in many cases not adequate to reach the therapeutic targets. One possible means of overcoming this limitation is to combine drugs with different mechanisms of action to obtain a synergistic effect on BP reduction. The more drug classes that are available, the more possibilities we have to obtain an effective BP control.

The article from Oliver et al published in this issue of Hypertension represents the first study performed with an accurate experimental design and methodology demonstrating that inhibitors of isoform 5 of phosphodiesterase (PDE) might be potentially used as a new drug class for the treatment of essential hypertension. PDE is a family of isozymes with various tissue and cellular distribution and linkage to specific cGMP- and cAMP-dependent pathways (Figure). To date, ≥11 PDE isoforms have been identified, and their tissue distribution together with the availability of specific antagonists is the basis for a potential clinical use of PDE inhibitors. PDE 5, a cGMP-hydrolyzing isoform, is highly expressed in vascular smooth muscle cells of the corpora cavernosa, but it is also well represented in various other tissues, including peripheral, coronary, and pulmonary vessels. Sildenafil is a specific inhibitor of PDE 5 isoform and, therefore, increases intracellular cGMP concentration by inhibiting its breakdown with the consequence of potentiating the cGMP-mediated reduction of intracellular calcium concentration (Figure). This effect is clinically useful in patients with erectile dysfunction, characterized by a reduced NO-dependent cGMP stimulation, but increasing evidence indicates that PDE 5 inhibition may be useful in treating other clinical conditions, including pulmonary hypertension and possibly essential hypertension. At the vascular level, because accumulation of cGMP can inhibit PDE 3, an isoform causing cAMP breakdown, sildenafil could also act theoretically by increasing cAMP, the effector of the adenyl cyclase–dependent relaxing pathway responsible for the vascular effects of several potent vasodilators, including isoproterenol, adenosine, papaverine, and dipyridamole (Figure). Considering that both PDE 3 and PDE 5 are present in vascular smooth muscle cells, sildenafil could directly increase cGMP and indirectly increase cAMP via cGMP-mediated PDE 3 inhibition.

However, despite this background, previous literature does not completely support the use of sildenafil as an antihypertensive drug, because studies were conducted with acute administration or in the presence of concomitant antihypertensive treatment. The strength of the study from Oliver et al derives from the correct methodology used to assess the BP-lowering effect of sildenafil in essential hypertension. The authors enrolled untreated essential hypertensive patients and used a randomized, crossover, double-blind experimental design to compare the hypotensive effect of sildenafil at 50 mg 3 times daily for 2 weeks and matched placebo. Active treatment significantly reduced both ambulatory and clinic BP by an extent similar to that observed with the other classes of antihypertensive drugs. It is worth noting that BP reduction induced by sildenafil was characterized by the absence of heart rate modifications. This observation is crucial, because the main limitation in the clinical use of direct vasodilators (and especially short acting molecules) is the sympathetic activation, which limits and sometime even abolishes the BP-lowering effect. Obviously, further studies are needed to identify the mechanism responsible for the lack of sympathetic activation and tachycardia evoked by sildenafil-induced BP reduction.

The second important aspect of the present study is the assessment of sildenafil effects on both arterial stiffening (assessed as central augmentation index and carotid-femoral pulse wave velocity) and endothelial dysfunction (assessed as brachial artery flow-mediated dilation [FMD]). Large arteries are important targets of essential hypertension, and prevention or reversal of vascular alterations can independently improve the prognosis of hypertensive patients. Treatment with sildenafil caused a slight decrease in central augmentation index. This effect was similar to that exerted on BP values and probably is related to reduction in peripheral vascular resistances, one of the principle determinants of peripheral arterial wave reflection. On the other hand, a lack of a specific effect of sildenafil on arterial stiffness seems to be supported by the absence of carotid-femoral pulse wave velocity modifications together with the finding that central BP was decreased by the active treatment to a similar extent as compared with peripheral BP. However, these results

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cannot be considered as conclusive, and further studies with a more prolonged sildenafil administration are probably needed, especially considering that nitrates, which directly increase cGMP concentrations, are highly effective in reducing arterial stiffness.9

Finally, the authors demonstrate that sildenafil does not improve endothelium-dependent vasodilation in the brachial artery of essential hypertensive patients.2 Sildenafil might improve endothelial function, because endothelial-derived NO acts on the smooth muscle cell by activating the cGMP pathway. However, this mechanism implies the presence of at least partially preserved NO availability. In patients with hypertension or cardiovascular disease, NO availability is impaired because of an excessive production of oxidative stress, and alternative pathways (hyperpolarization?) sustain endothelium-dependent vasodilation.10 Because the authors did not test NO availability by administration of a selective NO-synthase inhibitor, such as N^G-monomethyl-L-arginine, it is not possible to ascertain the NO contribution to endothelium-dependent vasodilation in the enrolled study population. It is conceivable that the negative results with sildenafil might indirectly suggest the presence of an almost totally compromised NO availability. Although these negative findings are at variance with some positive results, they have high relevance because of the state-of-the-art methodology used by the authors.

FMD is extensively used to assess conduit artery endothelial function, but the results produced with this technique are worthy of consideration only when specific methodologic requirements are satisfied. Basically, the low reproducibility of FMD can be improved by the use of a mechanical clamp to adjust and keep firm the ultrasound probe and by the application of a computerized system to continuously measure brachial artery diameter to detect the maximal vasodilation or calculate other important parameters, such as the area under the curve.11 Because the present results have been obtained with this kind of methodology, it is possible to state that sildenafil does not improve conduit artery endothelial function in essential hypertensive patients. However, because the endothelium is an autocrine/paracrine organ with several functions and different pathways, these negative results should not discourage continued investigation of the effect of PDE 5 inhibitors on other aspects of endothelial dysfunction.

In conclusion, the present study indicates that PDE 5 inhibition might be a valid option to reduce BP in hypertensive patients. Obviously this is only the beginning of the story, and a more complete development of sildenafil or other PDE 5 inhibitors as antihypertensive drugs is needed. Important issues to be addressed include: the use of slow-release formulations or compounds with long half-life to assure a homogenous BP-lowering effect lasting 24 hours; the demonstration of the safety of these drugs during long-term administration; and the evaluation of interactions with antihypertensive and nonantihypertensive drugs. A final and crucial aspect is the effect of PDE 5 on target organ damage. The results of this study do not support specific effects on conduit artery function. However, a prolonged treatment might give different results, especially on vascular structural changes, which are important alterations of hypertensive disease. In addition, the effect of PDE 5 inhibition on other major determinants of hypertensive organ damage, including left ventricular hypertrophy and microalbuminuria, needs to be assessed.1 If the story is to have a positive end, PDE 5 inhibitors may be a useful adjunctive drug class for the pharmacological treatment of essential hypertension and improved BP control in the general population.

**Disclosures**

None.

**References**


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