Sympathetic Activation by Sildenafil

To the Editor:

Phillips and colleagues report that administration of the specific type 5 phosphodiesterase (PDE5) inhibitor, sildenafil (100 mg), is associated with increased muscle sympathetic nerve activity (MSNA) at rest and in response to various stress stimuli in healthy young men.1 Because sildenafil did not alter mean heart rate or blood pressure, the authors conclude that sildenafil increases MSNA by direct central effects on sympathetic outflow.

Because sildenafil is a highly specific PDE5 inhibitor, its pharmacological actions should correspond to the tissue distribution of the PDE5 isoform. The references cited by the authors (reference numbers 17 and 18) to support their speculation regarding a direct central effect of sildenafil make no mention of the presence of PDE5 in the central nervous system. To our knowledge, there are no data which provide evidence of PDE5 in central cardiovascular control centers. To the contrary, where human tissue has been studied with histological techniques, PDE5 has been shown to be selectively expressed by smooth muscle cells and cells of smooth muscle origin, but not by striated muscle, cardiac myocytes, specialized conducting tissue, or peripheral neural tissue.2 The speculation that sildenafil has a direct central stimulatory effect is also inconsistent with recent studies that indicate that nitric oxide has sympatholytic properties.3

In view of the above considerations, the authors’ conclusions would be considerably strengthened by additional corroborative data correlating individual MSNA findings to blood pressure, catecholamine levels, vascular resistance changes, or other measures of autonomic function.

The ability to generalize the findings in healthy young men to cardiovascular disease populations must also be questioned. Although organic nitrates have also been reported to increase MSNA in young healthy subjects (as cited in reference number 26 of article), clinical trials of organic nitrates in cardiovascular disease populations have not demonstrated increased risk of adverse cardiac events. The authors’ concern regarding potential hypotensive effects of sildenafil in the setting of increased sympathetic drive, such as occurs in heart failure patients, appears to be unfounded, as a recent report indicates that sildenafil is well-tolerated in patients with heart failure with no significant changes in heart rate or blood pressure when compared with placebo.4

Further studies in cardiovascular disease populations are needed to determine whether beneficial effects of PDE5 inhibition on vascular function may offset potential adverse effects of reflex or direct sympathetic activation. Pending such investigations, published consensus recommendations provide guidelines for prudent clinical use of sildenafil in cardiovascular disease populations.5

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Response

We appreciate the interest of Drs Katz and Parums in our work.1 First, PDE5 is expressed in the penis, vascular smooth muscle, gastrointestinal tract, and the central nervous system.2,3 Accordingly, the main side effects of sildenafil include flushing, dyspepsia, visual disturbances, and headache.4 Human PDE5 mRNA was found to be the highest in the cerebellum, medulla, spinal cord, substantia nigra, and subthalamic nucleus as well as other areas of the brain to a smaller extent.3 Animal studies show PDE5 in Purkinje cell layers of the cerebellum.4 Second, given the limited understanding of the region-specific central neural effects of either NO or sildenafil, it may be an oversimplification to conclude that enhanced NO levels as a result of sildenafil must inhibit sympathetic activity. For example, injection of NO donors into the caudal ventrolateral medulla increases renal sympathetic nerve activity.5 However, we agree with the inference by Drs Katz and Parums that other explanations, such as potentiation of reflex responses, may cause sympathetic activation. Third, the limitations of extrapolating our data to patients with cardiovascular disease were clearly stated in our paper. Fourth, we reiterate that our study was not designed to show any link between sildenafil and cardiovascular risk, but rather to understand the physiological effects of sildenafil in healthy humans. Although nitrates and sildenafil may have the common qualitative effect of increasing sympathetic drive, and although nitrates may be used safely in many patients with cardiovascular disease, this surely does not imply that sildenafil can also be used with abandon in the same patients. Last, the paper by Katz et al6 evaluated resting measurements at one hour following a single dose of sildenafil in stable heart failure patients without prior intolerance to sildenafil. All cardiac medications were discontinued before the study. Although flow mediated dilation and blood pressure showed only modest changes following sildenafil, orthostatic blood pressure responses to sildenafil in heart failure patients on standard therapies would be germane to the question of sildenafil’s safety in this population. Also, maximal hemodynamic effects may occur early or up to several hours after sildenafil administration. A single measurement at one hour following sildenafil may be misleading.

We agree that there is much to be done and would be delighted should sildenafil prove to be safe and beneficial in heart failure.
patients across the board. For now however, pending more compelling data, we believe that sildenafil should be avoided in patients on nitrates and used with caution in patients with heart failure. This view is indeed consistent with the guidelines for prudent use of sildenafil.7

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