Non Erectile Dysfunction Application of Sildenafil

Bodo Cremers, Michael Böhm

Abstract
Sildenafil has proven effective in the therapy of male erectile dysfunction. However, little is known about other potential beneficial effects of sildenafil. Meanwhile, first observations have been made in numerous medical disciplines and disorders. Small doses of sildenafil may be a useful adjunct to inhaled iloprost in the management of pulmonary hypertension. In female sexual dysfunction and infertility, genital blood flow and endometrial thickening are enhanced after application of the compound. In gastrointestinal disorders, sildenafil also exerts several effects which might be of clinical relevance. In patients with heart failure, endothelial dysfunction is influenced by the phosphodiesterase-5 (PDE 5) inhibitor and exercise capacity might be improved. Moreover, in the treatment of Raynaud’s phenomenon, a disease without highly effective medical treatment option yet, first observations with sildenafil seem to be promising.

Key Words: Sildenafil · Viagra® · Pulmonary hypertension · Female sexual dysfunction · Infertility · Gastroenterology · Endothelial dysfunction · Heart failure · Cardioprotection · Raynaud’s phenomenon

Neue Anwendungsgebiete von Sildenafil

Zusammenfassung

Schlüsselwörter: Sildenafil · Viagra® · Pulmonale Hypertonie · Sexuelle Dysfunktion der Frau · Infertilität · Gastroenterologie · Endotheliale Dysfunktion · Herzinsuffizienz · Kardioprotektion · Raynaud-Syndrom

Introduction
Sildenafil (Viagra®) has proven effective in the therapy of male erectile dysfunction. The compound is a highly selective and potent inhibitor of the cyclic guanosine monophosphate-(cGMP-)specific phosphodiesterase-5 (PDE 5) isoenzyme [1]. Penile erection is mediated by nitric oxide (NO), which activates guanylate cyclase, an enzyme that converts guanosine triphosphate to cGMP. This second messenger then provides the signal for relaxation of both vascular and trabecular smooth muscle in the corpus cavernosum, with subsequent increased blood flow into the lacunar spaces. As cGMP is hydrolyzed by cyclic nucleotide PDE enzymes, sildenafil elevates the cGMP signal by inhibiting degradation of the guanosine nucleotide.
After its introduction, the drug has rapidly found widespread use and has meanwhile been prescribed successfully a million times in the treatment of erectile dysfunction. However, little is known about other potential beneficial effects of sildenafil. No doubt, PDE 5 has been detected at high concentrations in the corpus cavernosum [2] but is also known to exist in several other tissues [3]. Therefore, growing interest was accruing to examine the effects of sildenafil in various diseases different from male erectile dysfunction. Meanwhile, first observations have been made in numerous medical disciplines and disorders. This review gives some insight into the current status of the observations made so far in the non erectile dysfunction application of sildenafil and shows potential new therapeutic approaches for this interesting drug.

**Pulmonary Hypertension**

Primary pulmonary hypertension (PPH) is a progressive disease with a short life expectancy and a median survival of 2.8 years from the time of diagnosis [3] that often affects young people. Continuous infusion of epoprostenol (prostacyclin) has been shown to improve exercise capacity and survival markedly [4]. However, systemic application is limited by catheter infections, systemic hypertension, lack of selectivity for the pulmonary vasculature, and tachyphylaxis. By contrast, inhalation of aerosolized iloprost (a long-acting prostacyclin analog) causes preferential pulmonary vasodilation matched to ventilation and has been shown to improve exercise capacity and hemodynamics in patients with PPH [5]. However, due to the short-term effect, repetitive inhalations (six to twelve inhalations daily) are required to achieve sustained relief of pulmonary hypertension and is limited, like systemic application, by very high costs. One approach to prolong and to increase the effects of iloprost might be the concomitant use of PDE 5 inhibitors. The PDE 5 isoenzyme is abundantly expressed in lung tissue [6], and inhibition of cGMP breakdown might be particularly efficacious in pulmonary vasodilation, as cGMP formation is increased in patients with PPH [7].

Wilkins et al. [8] described the response to a combined treatment of sildenafil and nebulized iloprost in patients suffering from severe PPH with New York Heart Association (NYHA) stage III or IV. The short-term effects of 8.4–10.5 µg of aerosolized iloprost, cumulative doses up to 100 mg sildenafil, and the combination thereof were compared in five patients. Aerosolized iloprost resulted in a more pronounced decrease in mean pulmonary arterial pressure (PAP) than sildenafil alone (9.4 ± 1.3 vs. 6.4 ± 1.1 mm Hg, Figure 1a). The reduction in mean PAP after sildenafil was maximal after the first dose of 25 mg (Figure 1b). Interestingly, the combination of sildenafil plus iloprost lowered mean PAP significantly more than iloprost alone (13.8 ± 1.4 vs. 9.4 ± 1.3 mm Hg, Figure 1c). No significant changes in heart rate or systemic arterial pressure were observed during any treatment. However, pulmonary vascular resistance (PVR) was markedly diminished after iloprost inhalation, and cardiac output increased significantly. Again, sildenafil alone had similar effects on the latter parameters being already maximal after ingestion of the first dose of 25 mg. As for PAP, the combination of inhaled iloprost plus oral sildenafil pronounced and prolonged the effects on PVR and cardiac output. These data suggest that small doses of sildenafil may be a useful adjunct to inhaled iloprost in the management of pulmonary hypertension.

The latter study was recently confirmed by Ghofrani et al. [9] in a more heterogeneous group of patients with severe pulmonary hypertension due to PPH, chronic thromboembolic hypertension, CREST syndrome (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias), and aplasia of the left pulmonary artery. These data indicate that oral sildenafil is a potent pulmonary vasodilator that acts synergistically with inhaled iloprost also in secondary pulmonary hypertension. In an additional study, this working group could demonstrate that sildenafil is also capable of improving gas exchange in patients with severe lung fibrosis and secondary pulmonary hypertension [10]. Moreover, sildenafil has recently been shown to be effective also in the treatment of hypoxia-induced pulmonary hypertension [11], and first observations in the therapy of HIV-related pulmonary hypertension are likewise promising [12].

These data provide the basis for larger clinical trials in patients with pulmonary hypertension. Especially, little is still known about a sustained response to oral sildenafil in the long-term treatment of these lung diseases. However, smaller studies provide evidence for a substantial improvement in exercise ability and symptomatic benefit, which has been sustained at 3 and 6 months [13].

**Female Sexual Dysfunction and Infertility**

**Female Sexual Dysfunction**

Female sexual dysfunction (FSD) is age-related, progressive, and highly prevalent, affecting 30–50% of...