ABSTRACT

CHRONIC SILDENAFIL ENHANCES ERECTILE RESPONSES AND ENDOTHELium-DEPENDENT CORPORAL RELAXATIONS OF NORMAL RATS: LACK OF TACHYPHYLAXIS

Delphine Bebe-Roussel1, Diane Gorny1, Katell Mevel1, Stéphanie Caisse2 Jacques Bernaudeau1, Gillian Burgess2, Chris Wayman2, Laurent Alexandre1, François Giuliano1,3

1Pfizer France Laboratories, Gif-sur-Yvette, France 2 Pfizer Global Research and Development, Sandwich, UK 3Medical University of Paris South, Research Group in Urology, Le Kremlin-Bicêtre, France 4gilli@cyber-sante.org

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INTRODUCTION

Whether chronic treatment with sildenafil leads to tachyphylaxis has been a subject of debate. While some report a lack of tachyphylaxis in humans,4-6 others have suggested that chronic administration of sildenafil may lead to decreased efficacy.7-9 This study assessed the effects of an 8-week long chronic treatment with sildenafil (60 mg/kg/day SC three times a day) on intracavernosal pressure increase (expressed as ICP/MAP) elicited by electrical stimulation of the cavernous nerve and on endothelium-dependent relaxations of erectile tissue by in vitro isometric tension studies. The experiments were performed after a 36-hour washout period.

METHODS

Male Sprague-Dawley rats (180-220 g, n = 44) were anaesthetized with urethane (1.2 mg/kg). Evaluation of erectile function by simultaneous monitoring of the arterial pressure and intracavernosal pressure (ICP) following electrical stimulation of the cavernous nerve in vivo (square-wave pulses of 1 ms, duration of 45 s, 6 V at different frequencies (0-10 Hz) performed in a randomized manner and repeated twice in order to establish frequency-response curves)

RESULTS

- Male Sprague-Dawley rats (180-220 g, n = 44)
- Each experimental group received 20 mg/kg of sildenafil or saline solution via subcutaneous injection repeated three times a day (60 mg/kg/day in total) during 8 weeks
- Blood samples were collected before treatment, during the treatment period (8-month), 6-8 h after a subcutaneous injection and at the time of the in vivo experiments for the determination of free plasma concentrations of sildenafil (UK-92,480) and its active metabolite (UK-103,320)
- All experiments were performed after a 36-h washout period

CONCLUSION

A chronic treatment with sildenafil enhances erectile responses in anesthetized rats. The underlying mechanism for this absence of tachyphylaxis may be due to an upregulation of either muscarinic effect of chronic treatment with sildenafil on NO synthase/breakdown or on the subsequent guanylate cyclase activity.

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OBJECTIVES

- To study the effects of chronic treatment with sildenafil on the erectile responses elicited by electrical cavernous nerve stimulation in anaesthetized rats
- To investigate erectile responses before and after an acute administration of sildenafil in the chronically-sildenafil treated rats
- To evaluate the effects of chronic treatment with sildenafil on cavernosal tissue reactivity by in vitro isometric tension studies

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BACKGROUND

Although sildenafil has proven to be effective in treating ED, a report has suggested that its prolonged use may produce tachyphylaxis.

Lin et al., J. Urol. 2003

- BUT, large clinical trials including patients for long periods of time have demonstrated only very small patient dropout rates for lack of efficacy
- Moreover, despite broad clinical use and significant efficacy of sildenafil in the treatment of ED, certain patients with severe ED i.e. Erectile Function Domain Score from the IIEF below 11 remain poor responders
- Sildenafil could have additional and prolonged beneficial effects on endothelial function in diabetic patients if taken on a daily basis

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