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Although lower urinary tract symptoms (LUTS) are found in both sexes and women obviously do not have a prostate, LUTS in elderly males are often caused by a benign hyperplastic prostate (BPH) obstructing the cranial urethra [1]. This hyperplastic prostate comprises a proliferation of both glandular and smooth muscle tissue components. In theory, and possibly in daily life during each micturition in a man, this benign prostatic obstruction (BPO) can be overcome, at least partially, by a relaxation of the smooth muscle components of the prostate, thus relieving the obstructive periurethral ring [2].

As in many other smooth muscle tissues, prostatic smooth muscle relaxation is induced and maintained by the nitric oxide–phosphodiesterase–cyclic guanosine monophosphate/cyclic adenosine monophosphate (NO-PDE-cGMP/cAMP) pathway [3–5]. It has been shown that this signalling machinery is present in the human prostate and that NO relaxes precontracted prostatic tissue strips [2]. Similarly, the presence and the functional activity of various PDEs have been shown for human prostatic tissue [4–8]. Thus, we put forth the hypothesis that the use of a PDE-inhibitor in the human male with BPO should induce an increased relaxation of the prostate, resulting in a desobstruction of the BPO and possibly reduction of BPO-induced LUTS after some time.

As depicted by Giuliano in his editorial [9] and by others [10], all three approved PDE5-inhibitors were evaluated in large clinical studies for the indication of BPH. All three studies convincingly showed that LUTS were significantly alleviated by the regular use of a PDE5-inhibitor. Since many studies on medical treatment of BPH show a statistical significance for the active arm due to very high patient numbers included without any clinical significant effect over placebo, a subanalysis was done in our study; here, an important percentage of the patients showed an improvement in the International Prostate Symptom Score (IPSS) of 4 and more what is generally accepted as being clinically relevant [11].

Although the efficacy to improve LUTS was shown in all three PDE5-inhibitor studies, these studies failed to demonstrate a significant effect on the urinary flow [9,11]. This may be due to the fact that our hypothesis ("PDE5-inhibitors relax the prostatic smooth muscles, leading to a decreased prostatic infravesical obstruction") was wrong. Conversely, the missing effect on obstruction may be due to the fact that we included predominantly

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men without obstruction; thus, future planned studies on obstructed men will include pressure flow studies to further evaluate the effect of Vardenafil (and, most likely, for other substances) on BPO. Nature will tell us if the relaxation of prostatic smooth muscle cells by PDE5-inhibitors translate in desobstruction of men with BPO.

However, irrespective of the outcome of the evaluation of the “desobstruction hypothesis,” an effect of the PDE5-inhibitor on both the bladder wall smooth muscles as well as the afferent signalling pathway of the bladder is likely: PDE5 is heavily expressed in the smooth muscle cells of the bladder wall [12] and PDE5-inhibitors relaxed strips of bladder wall in the organ bath [13]. The importance of NO for the afferent signalling pathway [14] suggests that PDE5-inhibitors may be able to modulate this most important aspect of LUTS.

In summary, the available studies on the use of PDE5-inhibitors for the treatment of LUTS are promising; however, their efficacy for the treatment of BPO remains to be established.

Conflicts of interest

Dr Stief is a principal investigator for Bayer.

References


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