

Summary

Ian H. Osterloh

The discovery and development of VIAGRA® (sildenafil citrate)

Sildenafil citrate (Viagra®) is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the main regulator of cyclic guanosine monophosphate in human corpus cavernosum cells. Because PDE5 is found in vascular smooth muscle throughout the body, sildenafil was originally developed as a treatment for angina pectoris in the early 1990s by Pfizer scientists at their central research facility in Sandwich, UK. Phase I and II studies of sildenafil yielded only mild hemodynamic effects, although the side effect of erections was first noted. From the time of the first pilot studies investigating sildenafil as a treatment for erectile dysfunction (ED) in 1993, less than five years elapsed before the formal regulatory approval and launch of Viagra as the first effective oral treatment for ED in the spring of 1998. Sildenafil has now been prescribed to more than 20 million patients with ED worldwide, and the efficacy and safety profile has changed little since the time of first approval. Concomitant administration of nitrates or nitric oxide donors, however, does remain an important contraindication to sildenafil treatment.

Key Words: Clinical trials, drug development, erectile dysfunction, safety, sildenafil citrate.

Summary

Sharron H. Francis and Jackie D. Corbin

Sildenafil, pharmacology of a highly selective PDE-5 inhibitor

Prominence of PDE5 inhibitors in the treatment of male erectile dysfunction and other diseases related to vascular dysfunction mandates a comprehensive understanding of the properties and effects of these compounds. Sildenafil (Viagra™) was the first potent and selective PDE5 inhibitor to be widely marketed for clinical use. Its clinical efficacy and safety profile relates to its molecular mode of action, potency and selectivity for PDE5 as its target, and its pharmacokinetic properties (absorption, bioavailability, time to onset and duration of action, distribution, metabolism, and elimination). This Chapter focuses on the basic biochemical and pharmacological features of the interaction of sildenafil with PDE5 and the pharmacokinetic parameters that describe the action of sildenafil in facilitating smooth muscle relaxation leading to improved penile erectile response or causing side effects.

Key Words: Sildenafil, phosphodiesterase-5, PDE 5, male erectile dysfunction, PDE5 inhibitors, cGMP signaling, impotence, Viagra, cGMP, smooth muscle relaxation.

Summary

Culley C. Carson III

Sildenafil citrate: a 5-year update on the worldwide treatment of 20 million men with erectile dysfunction

(No summary available)

Summary

Francesco Montorsi, Alberto Briganti, Andrea Salonia, Patrizio Rigatti and Arthur L. Burnett

Current and future strategies for preventing and managing erectile dysfunction following radical prostatectomy

Introduction and objectives: As radical prostatectomy remains a commonly used procedure in the treatment of clinically localized prostate cancer, we critically analyzed current and future strategies for preventing and managing postoperative erectile dysfunction.

Methods: Systematic literature review using Medline and Cancerlit from January 1997 to June 2003. Abstracts published in the Journals European Urology, The Journal of Urology and the International Journal of Impotence Research as official proceedings of internationally known scientific Societies held in the same time period were also assessed.

Results: Patient selection and surgical technique are the major determinants of postoperative erectile function. Apoptosis of corporeal smooth muscle cells plays a role in the development of cavernous veno-occlusive dysfunction following radical prostatectomy. Pharmacological prophylaxis and treatment of postoperative erectile dysfunction is effective and safe. The concepts of cavernous nerve reconstruction and neuroprotection have been associated to promising results.

Conclusions: In the hands of experienced surgeons, properly selected patients undergoing a nerve sparing radical prostatectomy should achieve unassisted or medically assisted erections postoperatively.

Key Words: Erectile dysfunction, impotence, radical prostatectomy, prostate cancer.

Summary

Michael Müntener and Brigitte Schurch

Neurologic erectile dysfunction

Diseases and traumatic lesions of the nervous system often lead to some degree of erectile dysfunction, which usually adds significantly to the loss of quality of life associated with the respective condition. Apart from neurological physiology of male sexual function, this chapter covers the pathophysiology of male sexual dysfunction in spinal cord injuries, multiple sclerosis and Parkinson's disease.

Furthermore the most often used special tests and their respective roles in the diagnosis of neurogenic erectile dysfunction are discussed. Finally this chapter focuses on the treatment of neurologic erectile dysfunction and special emphasis is laid on first line medical therapy. The current literature on the use of Sildenafil in patients with erectile dysfunction associated with spinal cord injury, multiple sclerosis or Parkinson's disease is reviewed.

Key Words: Nervous system diseases, spinal cord injuries, multiple sclerosis, Parkinson disease, impotence, phosphodiesterase inhibitors.

Summary

Matthias J. Müller

Therapy of erectile dysfunction (ED) with sildenafil improves quality of life (QoL) and Partnership (QoP)

Erectile dysfunction (ED) is a highly prevalent and still undertreated condition. ED can have multiple etiologies or may be a symptom of an underlying illness. Untreated ED itself often

constitutes a chronic illness state with a strong negative impact on psychosocial health, quality of relationships, and quality of life. New oral treatment options with selective phosphodiesterase-(PDE)-5-inhibitors such as sildenafil have led to an increased awareness of ED and to a public discussion of their advantages, risks, and costs.

Studies for the treatment of ED with sildenafil in a broad spectrum of patient populations including patients with diabetes mellitus, chronic renal failure, kidney transplantation, spinal cord injury, prostate cancer, Parkinson's disease, and depression, have been conducted in the last few years. These studies have unequivocally shown that sildenafil is not only effective in improving erectile function, but also that this improvement is accompanied by improved quality of partnership (QoP), and quality of life (QoL). However, systematic studies investigating the partners of patients with ED are still scarce.

The empirical studies show impressively the positive impact of successful ED treatment with sildenafil on aspects of social life and psychosocial health. Thus, these data could help to overcome doubts and concerns regarding patients with ED seeking treatment and financial compensation.

Key Words: Quality of partnership, quality of life, erectile dysfunction, sildenafil, PDE5 inhibitors, depression.

Summary

Stuart N. Seidman

Erectile dysfunction, depression, and pharmacological treatments: biologic interactions

(No summary available)

Summary

Jennifer T. Anger and Jennifer R. Berman

Potential role for the PDE-5 inhibitor sildenafil in the treatment of female sexual dysfunction

The successful launch of sildenafil (Viagra[®], Pfizer) for the treatment of male erectile dysfunction has inspired an increasing research effort in the pathophysiology and potential for pharmacologic treatment of female sexual dysfunction. Recent clinical and animal research studies have demonstrated that sildenafil has a role in the treatment of female sexual arousal disorder (FSAD) by improving blood flow to the genital tissue. In a multicenter clinical trial of 201 postmenopausal women with female sexual arousal disorder (FSAD), sildenafil was shown to significantly improve sexual function. Sildenafil appears to have a better effect on sexual function in postmenopausal women taking long-term hormonal replacement therapy. Since estrogen replacement restores vaginal mucosal health, increases vaginal nitric oxide synthase expression, and decreases vaginal mucosal cell death, such a synergistic relationship between estrogen and sildenafil is expected. In addition, recent studies have demonstrated an improvement in sexual function in premenopausal women with and without sexual arousal disorder. Sildenafil may also represent an efficacious approach to the treatment of sexual dysfunction in women with neurologic disease, as well as women taking selective serotonin reuptake inhibitors (SSRIs).

Key Words: Viagra, sildenafil, phosphodiesterase-5 (PDE-5) inhibitors, female sexual dysfunction, female sexual arousal disorder, pathophysiology, menopause.

Summary

Graham Jackson

Sildenafil and cardiovascular events – drug interactions

The most common cause of erectile dysfunction (ED) is vascular endothelial dysfunction. Cardiovascular diseases share the same risk factors as ED – smoking, hyperlipidaemia, diabetes and hypertension – and the coexistence of a cardiac problem may cause concern with regard to advising on the treatment of ED. This concern has increased with the realisation that ED is a marker for previously undetected coronary artery disease and the casual use of sildenafil without proper assessment – so-called ‘internet sex’ – precipitating acute cardiac events.

In the era of evidence-based medicine, in order for all patients with coronary disease to maximise risk reduction they should be taking aspirin or clopidogrel, a statin, a beta blocker and an angiotensin-converting-enzyme inhibitor or angiotensin II antagonist. They may be on additional medication depending on their underlying problems or co-morbidities. The possibility of drug interactions is always a consideration when prescribing in general but will need additional thought with the intermittent use of sildenafil or the other phosphodiesterase type 5 (PDE5) inhibitors tadalafil and vardenafil. The casual user of sildenafil may be unaware of the possibility of drug interactions and present a clinical challenge if its use is not volunteered.

In this Chapter I will review the information we have on the presence or absence of significant PDE5 inhibitor drug interactions.

Key Words: Sildenafil, drug interactions, nitrate, nicorandil, nebivolol, alpha blocker, excretion.

Summary

Shadwan F. Alsafwah and Stuart D. Katz

Molecular processing of sildenafil in endothelial function: potential applications in cardiovascular diseases

Endothelial dysfunction plays an important role in the pathogenesis of hypertension, atherosclerosis, and chronic heart failure. Impaired endothelium-dependent vasodilation in patients with cardiovascular disease can be attributed to decreased bioavailability of nitric oxide and attenuated responses to nitric oxide in vascular smooth muscle. Impaired vasodilation in response to nitric oxide derived from vascular endothelium or organic nitrates may be related in part to increased degradation of the second messenger cyclic guanosine monophosphate by type 5 phosphodiesterase in vascular smooth muscle. Sildenafil, the first selective type 5 phosphodiesterase inhibitor approved for the treatment of erectile dysfunction, has been shown to acutely enhance endothelium-dependent vasodilation in patients with heart failure, coronary artery disease, and diabetes mellitus. Favorable hemodynamic effects have also been reported in patients with pulmonary hypertension. Further studies are warranted to characterize the safety and efficacy of type 5 phosphodiesterase inhibition in the treatment of cardiovascular diseases.

The vascular endothelium releases vasoactive substances that play an important role in the normal regulation of vasomotor tone in conduit and resistance blood vessels of the coronary, skeletal muscle, pulmonary, and other regional circulations [1]. This Chapter will review the role of the nitric oxide–cyclic guanosine monophosphate signaling pathway in the regulation of vasomotor tone in vascular smooth muscle and the potential therapeutic application of phosphodiesterase type 5 inhibition as a novel strategy to augment nitric oxide vascular signaling in cardiovascular disease populations.

Key Words: Endothelium, vascular heart failure, phosphodiesterase 5, nitric oxide, vasodilation.

Summary

Stephan Rosenkranz and Erland Erdmann

Cardiovascular safety of sildenafil in the treatment of erectile dysfunction

(No summary available)

Summary

Hossein Ardeschir Ghofrani, Werner Seeger and Friedrich Grimminger

NO pathway and phosphodiesterase inhibitors in pulmonary arterial hypertension

Pulmonary hypertension is a disease of various origins. Nitric oxide (NO), one of the most important endogenous vasodilators, plays a pivotal role in pulmonary vasoregulation. The signaling pathway of this mediator is mainly mediated by the guanylate cyclase-/cGMP-pathway with subsequent limitation of their action by enzymatic degradation through phosphodiesterases (PDE). Recent publications showed beneficial effects of the oral PDE-5 inhibitor sildenafil (currently approved for the treatment of erectile dysfunction (ED) only) for the treatment of various forms of pulmonary hypertension. The aim of the current summary is to give a brief overview about the experimental and clinical application of sildenafil in the field of pulmonary hypertension. This agent, despite oral application displays characteristics of a pulmonary selective vasodilator. Moreover, there is evidence that sildenafil is operative mainly in the vasculature of well ventilated areas of the lung. However, to date controlled randomized trials proving the efficacy of this approach for the treatment of pulmonary arterial hypertension are lacking. Before recommendations regarding therapy of this disease with PDE5 inhibitors can be made results of controlled trials have to be awaited.

Key Words: Pulmonary hypertension, pulmonary vasoregulation, NO/cGMP axis, PDE-5 inhibitor.

Summary

Udo Dunzendorfer, Arne Behm, Eva Dunzendorfer, Annette Dunzendorfer

The phosphodiesterase V inhibitor low responder study (PILRS) in patients with erectile dysfunction - A rationale for a PDE5 inhibitor combination therapy

Sildenafil citrate is definitely a progress in the molecular therapeutic approach of erectile dysfunction (ED) treatment. Urology has been equipped with a new drug which has been distributed worldwide within the shortest time possible. There are however failure rates immanent to the drug that need detailed analysis. The results of the PILRS study suggest using PDE5 inhibitors with a second drug in a constant combination to make the therapy safer and more effective. The rationale for PDE5 inhibitor combination therapy in patients with ED is presented.

Key Words: Non-responders to ED-therapy, clinical trials, drug development, dual drug therapy in ED, safety profile.

Summary

Mirko Mueller

Extended clinical use of sildenafil in patients with IPP, prostatitis and infertility syndrome

Patients presenting with IPP, Prostatitis or male infertility syndrome (MIS) frequently complain of ED in various clinical features. A stringent therapy with PDEV-inhibitors however has not been established so far. This contrasts to a large group of patients seen in the routine urology care unit where intermittent therapy by Sildenafil or analogues may promptly improve the psychological complex of these major urological diseases inducing greater health problems in younger patients as compared to the clinical profile of these diseases.

Key Words: IPP, prostatitis, male infertility syndrome, adjuvant therapy, role sildenafil.

Summary

Jan Dunzendorfer, Udo Dunzendorfer, Harald Förster

The cultural impact of sildenafil

Sildenafil – has it or has it not an impact on civilization? Only the future will answer this question. The importance of a serious drug is based upon thorough investigation and strict medical use, which in the case of sildenafil not necessarily contradicts to the application in life style medicine and wellness therapy.

Under different aspects one of the major interest is that sildenafil might be called a New Age drug in the present decline of culture in our affluent society in the 21st century.

Another aspect is to predict the role of sildenafil in a decade or two in the world. It may well be that sildenafil has become a daily use component in stabilizing the general vascular system and therefore has been well integrated.

Key Words: Non-responder, prevalence, epidemiology, Massachusetts Male Aging Study, Cologne Male Survey, National Survey of the Aging Male (MSAM-7), defective regional venous flow, multiple regulatory mechanisms, synchronization, prostaglandin, medical risk factor, high failure rate, combination therapy, new targets, sympathicomimetic compounds, integrated erection status (IES), open non-blind study, valid study population, identity of drugs, specific efficacy variables, two-sample *t*-test, sildenafil, DHE, DHE in the dual drug approach, ICH Guideline on Clinical Safety, adverse event, reintroduction of response to sildenafil, decrease of adverse events, adrenergic drugs, sphincter externus urethrae, pressure profile, NO, spermatic veins, pathological cavernosograms, varicocele, spermatozoa dysfunction, monovalent drug approach, abuse of PDE5 inhibitors, cardiac risk.



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