ERECTILE DYSFUNCTION:
COMPARISON OF EFFICACY AND SIDE EFFECTS OF THE PDE-5 INHIBITORS SILDENAFIL, VARDENAFIL AND TADALAFIL
REVIEW OF THE LITERATURE

U. Gresser[1], C. H. Gleiter[2]

[1]Praxisklinik Sauerlach, Internal Medicine, Germany,
[2]Department of Clinical Pharmacology, University of Tübingen, Germany

Abstract: Since introduction of the PDE-5 inhibitor sildenafil 4 years ago, there has been a fundamental change in the treatment of erectile dysfunction (ED). Intracavernosal or intraurethral injections of vasoactive substances or penile implants as mechanical aids now play hardly any part in it.

The development of the PDE-5 inhibitors vardenafil and tadalafil prompts the question of whether and how these three substances differ in terms of their efficacy and adverse effects.

Sildenafil has proven to be a very effective medicinal product. Studies with a follow-up period of up to 6 years have been conducted. The success rate of sildenafil varies in the group of ED patients with an organic underlying disease from 43% in patients who have undergone radical prostatectomy to 85% in patients with a neurological underlying disease, and amounts to an average 82% (range 43-85%, 100mg).

In an evaluation of spontaneous reports of deaths associated with sildenafil, the FDA concluded that there was no deducible evidence of an increase in the mortality rate among sildenafil users compared to the general population. In fact, fewer deaths associated in time with the ingestion of sildenafil were reported than might have been expected purely statistically on the basis of the normal mortality rate for men in this age group.

According to the initial studies conducted, vardenafil and tadalafil demonstrate efficacy data approximately comparable to those of sildenafil. As yet, insufficient data are available to evaluate the adverse effects of vardenafil and tadalafil, particularly their long-term use and use in high-risk groups.

Sildenafil has already been used by over 20 million men in over 110 countries and is one of the best-studied pharmacological substances available. This adventage in terms of knowledge and safety data makes sildenafil a safe and reliable treatment for patients with erectile dysfunction.

Key words: Sildenafil; vardenafil; tadalafil; erectile dysfunction

1. INTRODUCTION

According to epidemiological surveys, one in five men experiences impaired erection. Although these erection disorders have been used to be attributed mainly to psychogenic causes, they are now known to be mainly organic in origin, at least in the 50-plus age group.

Sexual dysfunction used to be, and still is in many societies, a taboo subject, and the scientific study of it was not pursued as vigorously as that of other medical conditions. This situation only changed with the market introduction of the first effective drug for the treatment of erectile dysfunction, sildenafil.

Since an effective oral drug treatment for erectile dysfunction has been available, treatments involving intracavernosal or intraurethral injections of vasoactive substances or penile implants as mechanical aids now play hardly any part.

Sildenafil and the substances vardenafil and tadalafil, which were developed later, are known as PDE-5 inhibitors. Sildenafil and vardenafil differ only minimally in terms of their structure, while tadalafil differs markedly from sildenafil and vardenafil in terms of its molecular structure, which is also reflected in pharmacokinetic differences.

The development of the PDE-5 inhibitors vardenafil and tadalafil now prompts the question of whether and how these three substances differ in terms of efficacy and adverse effects from sildenafil.

Since few full publications about tadalafil and vardenafil have been published, abstracts and poster publications will also be considered in the followig review.

Because patients ask for efficacy and side-effects of the new substances being informed by marketing reports in newspapers it is time to write this review now, based on the informations available for the public.

2. ERECTILE DYSFUNCTION

2.1. Physiology of Erections

The physiological process of erection is based on the interplay of neural, neurochemical and endocrinological mechanisms (Sachs 2000). The smooth muscle tone of corpus cavernosum and vascular system is controlled by complex biochemical processes, regulated by the peripheral and central nervous system. This takes place via neuroanatomical connections that constitute part of the innervation of the lower urogenital tract (Moreland et al. 2001).

In the healthy man, sexual stimulation triggers a release of the neurotransmitter nitric oxide (NO) from non-adrenergic, non-cholinergic (NANC) neurones that innervate the corpus cavernosum of the penis. NO effects intracellular activation of guanylate cyclase, which regulates the conversion of 5-GTP to 3`,5`-cGMP. cGMP mediates intracellular signal transduction, which leads via protein activation mechanisms to a reduction in the intracellular Ca^{++} concentration and so to relaxation of the smooth muscles in the penis, producing vasodilation and erection (Moreland et al. 2001).

2.2. Definition and Classification of Erectile Dysfunction

According to the internationally recognised definition of the National Institute of Health (NIH) in 1993, Erectile Dysfunction (ED) is defined as the persistent inability of a man to achieve and/or maintain an erection sufficient for a satisfactory sexual performance (NIH Consensus Statement of Impotence 1993).

ED can be classified according to its aetiology or severity. From an aetiological viewpoint, a distinction is made between an organic and psychogenic form, with the organic form being further differentiated according to vascular, neurogenic, anatomical and endocrinological causes. With the psychogenic form, a distinction is made between generalised and situation-dependent ED (Lizza and Rosen 1999). Besides a purely organic or purely psychological origin, mixed forms combining both causes frequently exist, and certain classes of drugs (e.g. beta-blockers, SSRI's, diuretics, etc) are also regarded as triggers of ED (Meinhardt et al. 1997). Erection disorders are subdivided into mild, moderate, or severe ED, according to the severity of the symptoms.

2.3. Prevalence of Erectile Dysfunction

The Massachusetts Male Aging Study (Feldman et al. 1994) found an ED prevalence of 52 % in 40 – 70-year-old men. Another US study (Laumann et al. 1999), the "National Health and Social Life Survey", noted that 31% of men in the 18 - 60 year age group had already experienced ED. In the German "Cologne Male Survey" (Braun et al. 2000), a significant age-correlated increase of 10% in the incidence of ED was found in men between the ages of 40 and 49, 16% in men between 50 and 59, 34% in men between 60 and 69, and over 50% in men between 70 and 80 years of age. The overall prevalence (age range 30-80 years) was 19.2%. Studies in England and France have yielded similar results (Spector and Boyle 1986, Giuliano et al. 1996). These results mean that almost one in five men experiences erectiles dysfunction.

Contrary to the earlier view that the cause of ED is predominantly psychogenic, it is now known to be due mainly to organic dysfunctions, at least in the 50-plus age group (Kaiser 1999).

2.4. Causes of Erectile Dysfunction

In most cases, erectile dysfunction is due to several causes. Cardiovascular risk factors are the most important. According to the Cologne study (Braun et al. 2000), 20% of ED patients suffer from diabetes mellitus, 30% from arterial hypertension, 30% are smokers and 38% regularly consume alcohol.

Similar results were also found by Pritzker (Pritzker 1999). According to his studies, 20% of ED patients show undiagnosed diabetes mellitus, 48% hypertension and 70% raised cholesterol levels. Similarly, Roumeguère et al. (2001) found diabetes mellitus in 20% of ED patients, hypertension in 26%, and hyperlipidaemia in 76%.

2.5. Therapeutic Options for Erectile Dysfunction

The first objective of every doctor is to cure the medical condition. Therefore, the primary goal in ED treatment is to determine the aetiology of the disease and treat it when possible, and not to treat the symptom alone. (Wespes et al. 2002). Nevertheless, it has been shown that treatment of organic risk factors alone often does not significantly improve the patient´s erectile function (Montorsi et al. 2002).

Oral drug treatments, the use of an erection-supporting vacuum pump and/or psychological sex therapy are symptom-orientated treatments available for erectile dysfunction (Montorsi et al. 2002). If none of these brings the desired success, treatment with intracavernosal or intraurethral injections of vasoactive substances can be attempted as second-line treatments (Montorsi et al. 2002). However, most patients find this a very unpleasant experience. Penis implants as mechanical aids play hardly any part in treatment since the introduction of sildenafil.

There are various approaches in drug treatment, which differ significantly in terms of their clinical efficacy.

For local use with intraurethral or intracavernosal injection (corpus cavernosum auto-injection therapy), the synthetic prostaglandin analogue (PGE1) alprostatil, for example, can be used. This treatment produces an erection by increasing the cAMP level in the corpus cavernosum (Andersson 2001).

In terms of oral therapeutic options, a fundamental distinction is made between a central and a peripheral action site.

The centrally acting substances available are the dopamine receptor agonist apomorphine and the selective alpha2 adrenoceptor blocker yohimbine.

Yohimbine acts both centrally as a noradrenergic agonist and peripherally as an alpha2 adrenoceptor blocker (Hatzichristou 2001). It has not yet been possible to demonstrate significant efficacy above the placebo level in a robust study. Accordingly, yohimbine has been classified as inadequately effective for the treatment of organic ED in the guidelines of the American Urology Association (Montague et al. 1996).

Apomorphine produces its effect by stimulating central dopamine receptors (predominantly D2) in the paraventricular nucleus of the hypothalamus, which activates pro-erectile pathway systems (including NO and oxytocin) and in this way produces an erection (Hatzichristou 2001). In a double-blind, placebo-controlled study by Dula et al. (2001), an erection firm enough for intercourse was obtained in 46.9 % of ED patients on apomorphine treatment, compared with a baseline figure of 21.9 %. In comparison with the placebo rate of 32.3 %, there is an absolute improvement of 14.6 %, which is not a satisfactory result. This is also evident in the low market share for apomorphine preparations, which in the case of Europe is less than 5 % (IMS data as at April 2002).

The most effective form of oral treatment are phosphodiesterase inhibitors, which will therefore be discussed in greater detail.

3. PHOSPHODIESTERASES AND THEIR INHIBITORS

To date, 11 PDE groups (PDE 1-11) are known, and these can be further differentiated into 21 sub-groups and about 53 splice variants.

Since these PDE forms are involved in the most diverse bodily functions in the form of in some cases very similar molecules, this raises the question of whether the PDE-5 inhibitors that are relevant to ED treatment also inhibit other phosphodiesterases. Table 1 provides an overview of the distribution of the PDE groups in the body and their possible functions (Francis et al. 2001, Osterloh 2001).

3.1. MECHANISM OF ACTION OF PDE-5 INHIBITORS

Phosphodiesterase inhibitors used for ED treatment are selective, competitive inhibitors of phosphodiesterase type 5 (PDE-5), an enzyme that breaks down cyclic guanosine monophosphate (cGMP) in various tissues, the second messenger of NO (Boolell et al. 1996). The selective and competitive PDE-5 inhibitor is sildenafil. PDE-5 inhibitors potentiate the muscle-relaxant effect of NO and are pharmacologically active only where cGMP synthesis is activated (e.g. through NO) (Ballard et al. 1998, Jeremy et al. 1997).

Following sexual stimulation, NO is released in the corpus cavernosum from nerves, vascular endothelium and smooth muscle cells, as a result of which the vessels in the penis and corpus cavernosum dilate, producing an erection (Burnett 1997). By inhibiting cGMP breakdown, PDE-5 inhibitors enhance the vasodilatory effect of NO and restore the ability to achieve an erection in patients with erectile dysfunc-tion.

3.2. PHOSPHODIESTERASE FAMILY

PDE-5 is a member of the phosphodiesterase family, which regulates multiple cell functions throughout the human body, by catalysing the breakdown of cGMP and cAMP. cGMP and cAMP are molecules of intracellular signal transduction that lead to protein phosphorylation, modulation of enzymes, ion channels, receptors and contractile proteins, through activation of protein kinase G.

The major function for phosphodiesterases in the cell is to terminate the cyclic nucleotide second messenger signal (Beavo et al 1995).

The cGMP level is a critical parameter for many cell functions, and is strictly regulated by a variety of control circuits in which phosphodiesterases play a central role. Much about this remains unexplained.

PDE-5 activity is controlled by at least two regulatory pathways.

The gene for all of the isoforms of PDE-5 known to date (A1-A2-A3) is found on chromosome 4q26 (Loughney et al. 1998, Yanka et al. 1998). In studies with human corpus cavernosum cell cultures, Lin et al were able to demonstrate that an increase in cGMP levels over 48 hours increases the activity of the PDE5A promoter gene and therefore PDE-5 expression or PDE-5 tissue levels (Lin et al. 2002).

Moreover, an increase in the cGMP level also leads to an increase in catalytic PDE-5 activity, with cGMP in conjunction with phosphokinase G and ATP leading to PDE-5 phosphorylation, which results in an increase in the cGMP binding capacity. By means of this mechanism, Corbin et al. (2000) were able to demonstrate a 50-70% increase in catalytic PDE-5 enzyme activity after an incubation time of only 1 hour.

Besides the increase in PDE-5 expression and the increase in catalytic activity (degradation pathway), the cGMP level can also be regulated via a change in cGMP synthesis. For example, Murthy was able to show by means of cell culture experiments that an increased cGMP level leads to a reduction in sGC synthesis via phosphokinase G-mediated phosphorylation of soluble guanylate cyclase (sGC) (Murthy et al. 2001).

On the basis of these results, the following hypothesis regarding the regulation of cGMP levels would be conceivable:

An increase in the cGMP level (e.g. through prolonged PDE-5 inhibition) leads to an increase in cGMP breakdown via an increase in PDE-5 activity and expression, and to a reduction in cGMP production via a reduction of sGC activity. The mechanisms described here then might lead to a reduction in the cGMP level in the form of counter-regulation.

Owing to the lack of sufficient long-term data, it is not yet possible to judge whether or not clinically relevant pharmacodynamic habituation occurs as a result of a chronic increase in the cGMP level, such as through the use of long-acting PDE-5 inhibitors like tadalafil.

Interesting long-term data for repeated use exist on

the assessment of the substance sildenafil. Sildenafil has been used in German clinical trials since 1995. In England, a small group of diabetes patients was treated for 6 years; 10 out of 11 were still very pleased with the success of the treatment 6 years later (Price 1999). In other studies, the long-term efficacy and tolerance of sildenafil were studied over a period of up to 3 years; 87-96% of ED patients proved to be pleased with sildenafil treatment, and the discontinuation rates due to lack of efficacy were, at 1-9%, very low (Montorsi et al. 2001, Steers et al. 2001, Gingell et al. 1999, Hackett 1999, Guliano et al. 1997, Christiansen et al. 2000, Hackett and Milledge 2001), so, at least for PDE-5 inhibitors with a relatively short half-life such as sildenafil, there is no evidence of a clinically relevant habituation effect.

3.3. Chemical Structure of cGMP and the PDE-5 Inhibitors Sildenafil, Vardenafil and Tadalafil

As competitive inhibitors of PDE-5, the chemical structures of the substances (Fig. 1) are very similar to that of cGMP. Sildenafil and vardenafil differ only minimally in terms of their structure, as a direct comparison of the structural formulas shows.

Tadalafil differs markedly from sildenafil and vardenafil in terms of its molecular structure, which is also reflected in marked pharmacokinetic differences.

3.4. Potency and Selectivity of PDE-5 Inhibitors

A review of the literature shows that the measured values for the potency and selectivity of PDE-5 inhibitors can vary, which can be demonstrated , for example, by the IC_{50} values (concentration at which the enzyme activity is 50% inhibited) of sildenafil (Table 2).

The reason for this is that IC_{50} values are dependent on the cGMP concentration, the source and extraction method of the enzymes, the reaction conditions, the number of samples, and other factors in the experimental design (Osterloh 2001). For this reason, different laboratories may obtain differing measure-

Table 1. Distribution and function of phosphodiesterases (Francis et al. 2001, Osterloh 2001)

| PDE isoenzyme/ substrate	Tissue distribution	Possible functional significance of PDE
PDE **1** / cGMP cAMP	Brain, heart, skeletal muscles, liver, vascular muscles, visceral muscles	Vascular muscular weakness, taste, olfaction
PDE **2** / cGMP cAMP	Adrenal cortex, corpus cavernosum, heart, visceral muscles, brain, skeletal muscles	Olfaction, adrenocorticosteroid production
PDE **3** / cGMP cAMP	Corpus cavernosum, heart, vascular and visceral muscles, blood platelets, liver, adipose tissue, kidney	Myocardial contractility; insulin secretion; lipolysis, glucoseproduction, platelet aggregation
PDE **4** / cAMP	Brain, testes, thyroid gland, kidney, lung, mast cells, skeletal muscles, vascular and visceral muscles	Inflammation; vascular and visceral muscle tone; depression, thyroid gland secretion, reproduction
PDE **5** / cGMP	Corpus cavernosum, vascular and visceral muscles, blood platelets	Erection; smooth muscle tone platelet aggregation
PDE **6** / cGMP	Retina (cones, rods)	Signal transduction in vision
PDE **7** / cAMP	Skeletal muscles, heart, lymphocytes	T-cell activation; skeletal muscles; metabolism
PDE **8** / cAMP	Widespread; e.g. testes, ovaries, bowel	T-cell activation
PDE **9** / cGMP	Widespread; most strongly expressed in the spleen, small intestine and brain	?
PDE **10** / cGMP cAMP	Brain (putamen and caudal nerve), testes, thyroid gland	Dopamine signal transmission
PDE **11** / cGMP cAMP	Skeletal muscles, heart, vascular muscles and visceral muscles (corpus cavernosum, prostate), pituitary gland, testes, liver and kidneys	?
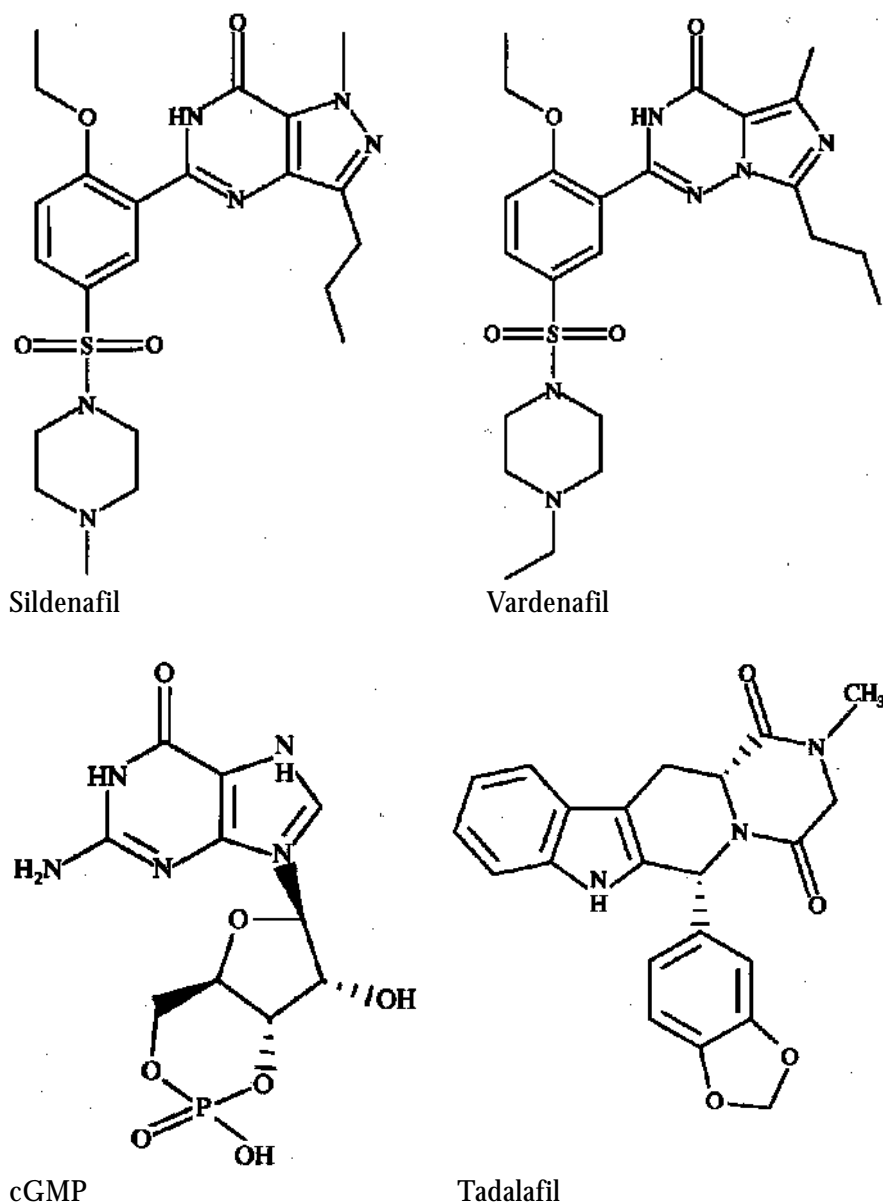
Fig. 1. Chemical structure of cGMP and the PDE-5 inhibitors sildenafil, vardenafil and tadalafil.

ment results, depending on the study conditions selected.

This lack of measurement precision concerns all PDE-5 inhibitors. The IC_{50} of tadalafil in terms of PDE-5 has been calculated as between 0.9 nM (Angulo et al. 2001) and 6.7 nM (Baxendale et al. 2001) and the IC_{50} of vardenafil between 0.1 nM (Philips et al. 2002) and 0.7 nM (Saenz de Tejada et al. 2001). Accordingly, vardenafil exhibits an PDE-5 inhibitory potential approximately five times higher than that of sildenafil , which is also reflected in the dosages used in clinical trials (5, 10 or 20 mg vardenafil versus dose strengths of 25, 50 and 100 mg sildenafil). For the assessment of efficacy and tolerance, it is therefore important to use equipotent dosages, i.e. to compare 20 mg vardenafil with 100 mg sildenafil, for example.

A single oral dose of 100 mg sildenafil produces a mean peak free sildenafil plasma concentration of 38 nM (EU-SPC VIAGRA). In order to achieve an inhi-

bition of some 90 % in PDE–5 activity, a free drug concentration of approximatelly 25 nM is necessary (Turko et al. 1999). PDE-5 is therefore already maximally inhibited by administration of 100 mg sildenafil (Gopal et al. 2001). This applies both in resting conditions and on stimulation of cGMP synthesis (e.g. through sexual activity). With this high efficacy, sildenafil sets the standard for other substances.

In relation to the binding potency of individual PDE-5 inhibitors to other PDE isoenzymes, there are no clear significant differences.

Considering selectivity for PDE 1-4 and 7-10 versus PDE-5, the substances discussed here show no relevant differences (Table 3).

Differences are apparent in terms of PDE-6, which plays an important role in the conversion of light impulses into nerve impulses in the retina. Here, sildenafil and vardenafil show lower selectivity than tadalafil. However, since peak plasma levels of 970 nM are reached after administration of 20 mg tadala-

Table 2. IC_{50} P values of sildenafil according to analyses by various laboratories.

Laboratory	$IC_{50 \text{ of }}$ sildenafil
Ballard et al. 1998	3.5 nM
Turko et al. 1999	4 nM
Saenz de Tejada et al. 2001	6.6 nM
Bischoff et al. 2001	8.5 nM

fil (Patterson et al. 2001), it remains to be seen whether or not PDE-6 might be inhibited by these substance under clinical conditions, something which cannot currently be assessed in view of the lack of published data on plasma protein binding and the free fraction.

A further difference exists in the area of PDE-11. Here tadalafil shows only 5 times greater selectivity with respect to PDE-5, which indicates inhibition of PDE-11 by tadalafil at clinical doses (Baxendale et al. 2001). PDE-11 inhibition by tadalafil could lead to adverse effects in clinical use. So far, PDE-11 has been detected in a variety of human tissues, e.g. in the heart, pituitary gland, brain and testes. The physiological significance of PDE-11 and the possible consequences of its inhibition have not yet been established. There is a marked difference of tadalafil versus sildenafil and vardenafil. Sildenafil and vardenafil are not expected to inhibit PDE-11.

3.5. PHARMACOKINETICS

All three substances are rapidly absorbed from the gastrointestinal tract, with peak plasma levels being attained within 1 hour in the case of sildenafil (Milligan et al. 2002) and vardenafil (Sachse and Rohde 2000) and after 2 hours in the case of tadalafil (Patterson et al. 2001), with a range of 0.5 – 12 hours for tadalafil. Absorption takes place mainly from the small intestine, with the gastric emptying time playing an important role in the onset of action.

According to the current publication situation, food intake causes no delay or reduction in tadalafil absorption (Ibid 2001), whereas it is known to reduce and delay sildenafil absorption (Nicols et al. 2002). Since, at a therapeutic dosage, sildenafil has adequate latitude in terms of maximum inhibition of PDE-5, a good clinical effect is also obtained on ingestion after food intake. Ingestion on an empty stomach produces a more rapid onset of action, whereas ingestion after or with a meal produces a slower onset of action (Corbin and Francis 2002).

The bioavailability of sildenafil is approx. 41 % (Nichols et al. 2002). After a single oral dose of 100 mg sildenafil, a total mean plasma concentration of approximatelly 440 ng/ml is achieved, the plasma protein binding is 96 %, which means that there is a mean free sildenafil peak plasma concentration of 18 ng/ml. For tadalafil (20 mg) and vardenafil (20 mg) total mean plasma concentrations are 378 ng/ml (Patterson et al. 2001) respectively 19 ng/ml (Sachse and Rhode 2000). Data concerning plasma protein binding or mean free peak plasma concentrations have not yet been published.

The mean half-lives of sildenafil and vardenafil are 3 - 4 hours (Sachse and Rohde 2000) and that of tadalafil, approximatelly 18 hours (Patterson et al. 2001). Tadalafil can still be detected in the blood 5 days after ingestion (Patterson et al. 2001), which means that accumulation might be possible, if tadalafil would be taken regularaly and in short intervals.

Approximatelly 50 % of all drugs are metabolised via the cytochrome-P 450 system (Eichelbaum and Burk 2001), which exhibits a great deal of genetic polymorphism. The elimination of sildenafil (Hyland et al. 2001), vardenafil (Rohde et al. 2001) and tadalafil ((Patterson et al. 2001) takes place overwhelmingly

Table 3. Selectivity of sildenafil, vardenafil and tadalafil with reference to the various PDE groups (Phillips et al. 2002, Ballard et al. 1998).

PDE groups	Sildenafil IC_{50} Nmol (x fold selectivity)	Vardenafil IC_{50} Nmol (x fold selectivity)	Tadalafil IC_{50} Nmol (x fold selectivity)
PDE1	281 (80)	70 (500)	>30000 (>4450)
PDE2	>30000 (>8570)	6200 (44290)	>100000 (>14800)
PDE3	16200 (4630)	>1000 (>7140)	>100000 (>14800)
PDE4	7680 (2190)	6100 (43570)	>100000 (>14800)
PDE5	**3.5 (1)**	**0.14 (1)**	**6.7 (1)**
PDE6 (rods)	**37 (11)**	**3.5 (25)**	**1260 (187)**
PDE6 (cones)	**34 (10)**	**0.6 (4)**	**1300 (193)**
PDE7A	21300 (6090)	>30000 (>214000)	>100000 (>14800)
PDE8A	29800 (8510)	>30000 (>214000)	>100000 (>14800)
PDE9A	2610 (750)	581 (4150)	>100000 (>14800)
PDE10A	9800 (2800)	>3000 (>21200)	>100000 (>14800)
PDE11A	**2730 (780)**	**162 (1160)**	**37 (5)**

via the liver, mostly via the cytochrome enzyme P450 (CYP3A4). CYP3A4 expression varies up to a factor of 50 between various individuals, and in vivo enzyme function by at least a factor of 20 (Özdemir et al. 2000).

4. CLINICAL EXPERIENCE

4.1. ONSET OF EFFECT AND DURATION OF EFFECT

In humans, the mean onset of effect of sildenafil takes place approximately 27 min. after ingestion (Eardley et al. 2002); in the rabbit vardenafil acts approx. 20 min. afterwards, the maximum vardenafil effect takes place after 45 to 90 min. (Bischoff et al. 2001).

An initial onset of action 16 min. after ingestion has been described for tadalafil in a highly preselected population (Padma-Nathan et al. 2001); for sildenafil, too, efficacy has been demonstrated only 12 minutes after ingestion (Eardley et al. 2002). Peak plasma tadalafil levels (Patterson et al. 2001) are reached after two hours on average. In one study of tadalafil (25 mg) in 61 men, adequate efficacy was found in the majority of patients after 30 to 120 min..However, 24 h after ingestion of tadalafil (10 and 20 mg respectively) some effect was still apparent (Padma-Nathan et al. 2001).

4.2. EFFICACY

According to the study results available to date, all three PDE-5 inhibitors are effective.

Owing to the lack of direct comparative studies, any comparison of the clinical effect of the substances relies on the comparison of different, not directly comparable, studies, which is difficult because the target criteria and patient selection criteria are not uniform.

In some cases, sildenafil non-responders were excluded from studies with vardenafil (Porst et al. 2001, Brock et al. 2001) and tadalafil (Brock et al. 2002), which makes it practically impossible to compare response rates. For this reason, a sensible comparison criterion would appear to be a change in erectile function versus the baseline value in comparison with placebo, which was recorded uniformly in all of the studies using the IIEF questionnaire (IIEF = International Index of Erectile Function).

Treatment with vardenafil in a dose of 20 mg produced an improvement in the ability to achieve an erection in 80 % of ED patients (Porst et al. 2001). In a comparable study of sildenafil (100 mg dose) by Goldstein, 84 % of ED patients were successfully treated (Goldstein et al. 1998). Treatment with tadalafil 25 mg produced an improvement in the ability to achieve an erection in 81 % of ED patients (Padma-Nathan et al. 2001). Therefore, sildenafil, at 84 %, is slightly more effective than vardenafil at 80 % and tadalafil at 81 %. If efficacy is compared versus placebo, the differences between sildenafil and the two other substances are even clearer. In comparison with placebo, treatment with 100 mg sildenafil leads to a 20-fold improvement in IIEF question 3 (when you attempted sexual intercourse, how often were you able to penetrate your partner?), treatment with 20 mg vardenafil to a 7.5-fold improvement, and treatment with 25 mg tadalafil to a 1.4-fold improvement compared to initial value.

4.3. TOLERANCE

Typical side effects of PDE-5 inhibitors are headache, facial flushing, nasal congestion, and dyspepsia. According to the current publication situation, desired and undesired effects can be assumed to be similarly frequent, similarly severe and similarly dose-dependent for all three PDE-5 inhibitors. As yet, the published data on the two more recent substances remain insufficient to reach a conclusive assessment of the adverse effects. In particular, there is a lack of large, double-blind, randomised comparative studies. It would be particularly interesting to establish whether the relatively long elimination half-life of tadalafil or the low bioavailability of vardenafil is associated with a greater number of adverse effects.

Both sildenafil and vardenafil weakly inhibit PDE-6. Changes in vision have been described - rarely - for both substances in relatively high dosages (Porst et al. 2000, Sachse and Rohde 2000). Experience with sildenafil has shown that only a few patients discontinue treatment for this reason (Laties et al. 2000, Zrenner et al. 2000). Long-term studies with sildenafil have produced no evidence of more extensive or permanent disturbances of the visual system as a result of occasional PDE-6 inhibition (Wallis et al. 1998, Grunwald et al. 1999). Similar data is not yet available for vardenafil. In the case of sildenafil, patients with retinitis pigmentosa, a rare hereditary disease, are excluded from treatment for drug safety reasons.

Tadalafil is a potent PDE-11 inhibitor , found, amongst other places, in the smooth muscles of the internal organs, cardiac and skeletal muscles, pituitary gland, Leydig's cells and germ cells in the testes (Baxendale et al. 2001, Osterloh 2001). The physiological significance of the enzyme and the possible consequences of its short-term or medium-term inhibition have not yet been established. The back and muscle pain reported relatively frequently with tadalafil (Porst 2000) may be associated with this.

Tolerability of tadalafil is problematic: with daily ingestion, 7 % of patients in the 10 mg group discontinued treatment owing to side effects, 10 % at 25 mg, 19 % at 50 mg and 29 % at 100 mg. With ingestion on demand, tadalafil caused muscle and back pain in over 10 % of those treated and dyspepsia and headache in over 25 % (Porst 2000).

4.4. INTERACTIONS

All PDE-5 inhibitors act in a similar way via the NO/cGMP mechanism described at the beginning. For this reason, tadalafil and vardenafil can be assumed to potentiate the hypotensive and anticoagulant effect of nitrates and NO donors, as is already known to occur with sildenafil. Vardenafil and tadala-

fil potentiate the vasodilatory effect of NO donors (Angulo et al. 2001a and b, Bischoff et al. 2001). In patients who are being treated with them, none of the three PDE-5 inhibitors is advisable.

For sildenafil detailed informations are published in the Standard Product Characteristics (EU-SPC Viagra).

Since all 3 substances are broken down mainly via cytochrome P450 CYP3A4, a dose adjustment should be considered when given in combination with CYP3A4 inhibitors (e.g. HIV protease inhibitors, erythromycin, ketoconazole).

4.5. HIGH-RISK GROUPS

Like sildenafil, vardenafil has a slightly hypotensive effect, maximal 5-10 mmHg average (Sachse and Rohde 2000). An increase in the heart rate has been described at a vardenafil dose of 40 mg (Sachse and Rohde 2000).

Since peak vardenafil levels are 30 % higher in elderly patients and the half-life is 25 % longer (Porst et al. 2001), low dosages should first be used in this patient group. At the high dose of 20 mg vardenafil, adverse effects were reported twice as frequently in elderly patients with 63 % (Porst et al. 2001).

Tadalafil, too, exhibits a 28 % longer half-life, i.e. 22 hours, in elderly patients. In elderly men, the substance was still detectable 6 days after ingestion. Impaired hepatic and renal function also produced an additional lengthening of the half-life of the substance. Furthermore, smoking and the body mass index had a weak effect on the pharmacokinetics of tadalafil (Patterson et al. 2001) whereas food intake had no effect (Patterson et al. 2001).

Both diabetes mellitus and sexual intercourse are associated with an increased risk to get a cardiovascular event. For vardenafil serious adverse events have been reported in diabetes patients (placebo: 1 %, 10 mg: 2 %, 20 mg: 3 %) (Goldstein et al. 2001).

The availability of the new PDE-5 inhibitors has led to an intensive discussion of the differences in efficacy and the side effect rate in comparison to sildenafil, particularly with respect to the frequency of any cardiovascular events. In the first phase of the Prescription Event Monitoring study, it became clear that myocardial infarctions and deaths as a result of coronary heart disease were not observed more frequently in sildenafil users than in the general population, even in widespread use - when prescribed by doctors in general practice without any formal inclusion and exclusion criteria (Shakir et al. 2001). Age-standardised mortality and morbidity rates produce no evidence of an increased risk of myocardial infarction or deaths as a result of coronary heart disease in sildenafil patients.

In an FDA publication (Wysowski et al. 2002), a conclusive evaluation of spontaneous reports of deaths associated with sildenafil was undertaken. The authority came to the conclusion that no evidence of an increased mortality rate among sildenafil users compared to the general population could be deduced from the spontaneous reports. In fact, fewer deaths associated in time with the ingestion of sil-

denafil were reported than might have been expected purely statistically on the basis of the normal mortality rate for men in this age group.

4.6. CONTRAINDICATIONS

For all three substances contraindications are similar.

Patients in whom sexual activity is not advisable on medical reasons (e.g. patients with severe cardiovascular disease) should not be given ED treatment (DeBusk et al. 2000). In some circumstances, abstaining from sexual activity may save the lives of these patients - even though they have to forego some of the pleasure of sexual activity. For the same reason, patients who have recently experienced a heart attack or stroke should be excluded from ED treatment.

In patients receiving nitrate or NO-donors treatment with PDE-5 inhibitors is contraindicated.

Since both sildenafil and vardenafil have moderate vasodilatory and hypotensive effects, they should not be given in the presence of marked arterial or orthostatic hypotension, and should only be administered with caution in aortic stenosis or hypertrophic obstructive cardiomyopathy. Further studies are needed to clarify whether tadalafil affects the circulatory system less owing to its slower pharmacokinetics.

Patients with retinitis pigmentosa should not be treated with a PDE-5 inhibitor.

Patients receiving nitrate or NO-donor treatment, and those who have experienced significant cardiac events in the previous six months, suffer from proliferative retinopathy or retinitis pigmentosa have been excluded from studies with vardenafil (Goldstein 2001, Porstet al. 2001, Klotz et al. 2001), something which is scientifically logical and ethically correct. Even more caution has been exercised in studies with tadalafil - all patients with signs of clinically relevant liver, kidney or coronary artery disease, cardiovascular disease or CNS disturbances in the last six months have been excluded (Porst 2000, Brock et al. 2001).

This is to be acknowledged as morally and ethically positive, but it does make it more difficult to compare the new substances with sildenafil, which - being the first PDE-5 inhibitor in clinical use - has been studied in considerably wider-ranging patient populations. There are sufficient data on sildenafil to confirm that it does not lead to an increase in the mortality rate compared with the general population (Wysowski et al. 2002). It is not possible to comment on vardenafil and tadalafil in this regard, owing to the lack of study data.

5. CONCLUSION

As knowledge stands at present, PDE-5 inhibitors are the method of choice for the treatment of erectile dysfunction, alongside treatment for the underlying disease.

Sildenafil has proven to be an effective and well tolerated drug. Studies with a follow-up period of up to 4 years have been conducted. The success rate of sildenafil varies in the group of ED patients with an or-

ganic underlying disease between 43% in patients who have undergone radical prostatectomy and 85% in patients with a neurological disease, and amounts to a mean of 82% (Guay et al. 2001). The treatment success rate can be increased by repeated usage attempts (McCullough et al. 2001).

Vardenafil and tadalafil demonstrate efficacy data that can be presumed to be approximate to those of sildenafil. Since near maximum inhibition of PDE-5 is already achieved with sildenafil (Turko et al. 1999), an increase in efficacy is not to be expected with vardenafil and tadalafil.

As yet, we need more data to assess the adverse effects of vardenafil and tadalafil, particularly in long-term use and in high-risk groups.

Sildenafil has already been used in over 20 million men in over 110 countries (Pfizer Inc. data on file) and is one of the best studied pharmacological substances around. For example, 1095 scientific publications are available on Medline, the database of the National Institute of Health, using the keyword sildenafil, 24 publications using vardenafil and 3 publications using tadalafil (as at August 25, 2002). Some 4 years after the market launch of sildenafil, the post-marketing data show a high degree of concordance with the efficacy and safety data obtained in the clinical licensing studies (Sadovsky et al. 2001).

The Office of Drug Safety of the FDA (Federal Drug Administration) collected and analyzed reports of death in men prescribed sildenafil from its marketing in March 1998. In conclusion there did not appear to be an increase in death due to myocardial infarction above expected numbers in the same age groups compared to sildenafil users (Wysowski DK et al. 2002).

This advantage in terms of knowledge and safety data makes sildenafil a safe and reliable treatment for patients with erectile dysfunction.

Whether tadalafil or vadenafil are complementary to sildenafil or not will be shown the years following market introduction.

REFERENCES

Andersson K-E. Wagner G: Physiology of erection. Physiol Rev 75, 1995: 191-236

Andersson K-E. Pharmacology of penile erection. Pharmacol Rev 2001; Vol. 53: 417-450

Angulo J, Cuevas P, Fernandez A et al. Characterization of Vardenafil, a new PDE5 inhibitor for erectile dysfunction, and comparison of activity with Sildenafil. Poster, presented at ESSIR, Rome 2001

Angulo J, Gadau M, Fernandez A et al. IC351 enhances NO mediated relaxation of human arterial and trabecular penile smooth muscle. Poster, presented at ESSIR, Rome 2001

Ballard SA, Gingell CJ, Tang K et al. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. J Urol 1998; 159: 2164-2171

Baxendale RW, Burslem F, Phillips SC. Phosphodiesterase type 11 (PDE 11) cellular localisation: progress towards defining a physiological role in testis and / or reproduction. Poster, presented at AUA, Anaheim 2001

Baxendale RW, Smith EJ, Stanley M et al. Selectivity of sildenafil citrate and other phosphodiesterase type 5 inhibitors against human PDE types 7-11. Poster, presented at AUA, Anaheim 2001

Baxendale RW, Wayman CP, Turner L et al. Cellular localisation of Phosphodiesterase Typ 11 (PDE11) in human corpus cavernosum and the contribution of PDE11 inhibition on nerve stimulated relaxation. Poster, presented at AUA, Anaheim 2001

Beavo JA. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. Physiological Reviews 1995 Oct.; Vol.75: No. 4

Bischoff E, Niewoehner U, Haning H et al. The oral efficacy of Vardenafil for inducing penile erection in a conscious rabbit model. J Urol 2001; 165:1 316-1318

Bischoff E, Niewoehner U, Haning H et al. The inhibitory selectivity of Vardenafil on bovine and human recombinant phosphodiesterase isoenzyme. Poster, presented at AUA, Anaheim 2001

Bischoff E, Palau P, Mondritzki T et al. Comparison of the oral efficacy of Vardenafil, a new highly selective PDE-5 inhibitor, and Sildenafil in inducing penile erections in a conscious rabbit model. Poster, presented at ESSIR, Rome 2001

Boolell M, Allen MJ, Ballard SA et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. Int J Impot Res 1996; 8: 47–52

Braun M, Wassmer G, Klotz T et al. Epideminology of erectile dysfunction: results of the „Cologne Male Survey". Int J Imp Res 2000; 12: 305-311

Brock G, Iglesias J, Toulouse K et al. Efficacy and tolerability of Vardenafil in Males with ED following radical Prostatectomie. Poster, presented at ESSIR, Rome 2001

Brock G, Taylor T, Seger M: Efficacy and safety of IC351 treatment for ED. Poster, presented at ESSIR, Rome 2001

Burnett AL. Nitric oxide in the penis: physiology and pathology. J Urol 1997; 157: 320–324

Carson et al. Textbook of Erectile Dysfunction. Oxford: Isis Medical Media, 1999: xvii-xviii

Christiansen E, Guirguis WR, Cox D et al. Long-term efficacy and safety of oral VIAGRA® (sildenafil citrate) in men with erectile dysfunction and the effect of randomised treatment withdrawal. Int J Impot Res 2000; 12: 177-182

Corbin JD, Francis SH: Pharmacology of Phosphodiesterase-5 inhibition and treatment of erectile dysfunction. Poster presented at AUA 2002, Orlando

Corbin JD, Turko IV, Beasley A, et al. Phosphorylation of phosphodiesterase-5 by cyclic nucleotide-dependent protein kinase alters its catalytic and allosteric cGMP-binding activities. Eur J Biochem 2002; 267: 2760-2767

DeBusk R, Drory Y, Goldstein I et al. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton consensus panel. Am J Cardiol 2000; 86(2): 175-181

Dula E, Bukofzer S, Perdok R et al. Double-blind, crossover comparison of 3 mg apomorphine SL with placebo and with 4 mg apomorphine SL in male erectile dysfunction. Eur Urol 2001; 39: 558-564

Eardley I, Ellis P, Boolell M et al. Onset and duration of action of Sildenafil citrate for the treatment of erectile dysfunction. Br J Clin Pharmacol 2002; 53: 61S-65S

Eichelbaum M, Burk O: CYP3A genetics in drug metabolism. Nature Medicine 2001; 7: 285-287

Feldman HA, Goldstein I, Hatzichristou DG et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994; 151: 54–61

Francis SH, Turko IV, Corbin JD: Cyclic nucleotide phosphodiesterases: relating structure and function. Prog Nucleic Acid Res Mol Bio 2001; 65: 1-52

Gingell C, Buvat J, Jardin A et al. Sildenafil, an oral treatment for erectile Dysfunction: A 1-year, open-label, extension study. IJCP 1999; Supp102: 30 – 31

Giuliano F, Jardin A, Gingell CJ et al. Sildenafil (VIAGRATM), an oral treatment for erectile dysfunction: A 1-year open-label, extension study. Br J Urol 1997; 80: 366

Giuliano FA, Knelleson S, Paturaud JP: Epidemiologic study of erectile dysfunction in France. Eur Urol. 1996; 30(suppl 2): 250

Goldstein I, Lue TF., Padma-Nathan H et al. Oral Sildenafil in the treatment of erectile dysfunction. NEJM 1998; 338: 1397-1404

Goldstein I, Young JM, Fischer J et al. Vardenafil, a new highly selective PDE5 inhibitor, improves erectile function in patients with diabetes mellitus. Poster, presented at ADA, Philadelphia 2001.

Goldstein I: Vardenafil demonstrates improved erectile function in diabetic men with erectile dysfunction. Poster, presented at ESSIR, Rome 2001

Gopal VK, Francis SH, Corbin JD: Allosteric sites of phosphodiesterase-5 (PDE5). Eur. J. Biochem 2001: 268: 3304-3312

Grunwald JE, Koppiker NP, Hodges M: Visual adverse events in patients with eye disorders who received Sildenafil for the treatment of erectile dysfunction. Invest Ophtalmol Vis Sci 1999; 40(4): S766 (# 4048)

Guay AT, Perez JB, Jacobson J et al. Efficacy and safety of Sildenafil citrate for treatment of erectile dysfunction in a population with associated organic risk factors. Journal of Andrology 2001; 22: 793-797

Hackett G, Milledge D: Twelve month Follow-up of Consecutive ED 260 Patients treated with VIAGRA®. West Midlands, UK; presented ESSIR, Rom 2001

Hackett G: Long-term safety and efficacy after 2 years of VIAGRA® treatment in ED. The Journal of Urology 1999; 161 (Supp4): 214

Hatzichristou DG, Pescatori ES: Current treatments and emerging therapeutic approaches in male Erectile Dysfunction. BJU 2001; 88 (Suppl.3): 11-17

Hyland R, Roe EGH, Jones BC et al. : Identification of the cytochrome P450 enzymes involved in the N-demethylation of sildenafil. Br J Clin Pharmacol 2001, 51, 239-248

Ibid (Pressemitteilung Lilly ESSIR Rom 2001)

IMS Daten Stand April 2002

Jeremy JY, Ballard SA, Naylor AM et al. Effects of sildenafil, a type-5 cGMP phosphodieasterase inhibitor, and papaverine on cyclic GMP and cyclic AMP levels in the rabbit corpus cavernosum in vitro. Br J Urol. 1997; 79: 958–963

Kaiser FE : Erectile dysfunction in the aging man. Med. Clin North Am 1999; 83: 1267-1278

Klotz T, Sachse R, Heidrich A et al. Vardenafil increases penile rigidity and tumescence in erectile dysfunction patients: a RigiScan and pharmacokinetic study. World J Urol 2001; 19: 32-39

Laties AM, Koppiker NP, Smith MD: Characterization of visual adverse events after dosing with Sildenafil citrate. Invest Ophthalmol Vis Sci 2000; 41(4): S592 (# 3148)

Laumann EO, Paik A, Rosen RC: The epidemiology of erectile dysfunction: results from the National Health and Social Life Survey. Int J Impot Res 1999; 11 (Suppl.1): S60-64.

Lin CS, Chow S, Lau A, Tu R, Lue TF: Human PDE5A gene encodes three PDE5 isoforms from two alternate promoters. Int J Imp Res 2002; 14: 15-24

Lizza EF, Rosen RG. Definition and classification of erectile dysfunction: Report of the Nomenclature Committee of the International Society of Impotence Research. Int J Imp Res 1999; 11: 141-143

Loughney K, Hill TR, Florio VA et al. Isolation and characterization of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3′, 5′-cyclic nucleotide phosphodiesterase. Gene 1998; 216: 139-147

McCullough AR, Siegel RL, Shpilsky AB: Intercourse success rates with sildenafil citrate. J Urol 2001; Vol. 165, No.5: (Suppl) # 699

Meinhardt W, Kropman RF, Vermeij P et al. The influence of medication on erectile function. Int J Imp Res 1997; 9: 17-26

Milligan PA, Marshall SF, Karlsson MO: A population pharmacokinetic analysis of Sildenafil citrate in patients with erectile dysfunction. Br J Clin Pharmacol 2002; 53: 45S-52S

Montague DK, Barada JH, Belker AM et al. Clinical guidelines panel on erectile dysfunction : summary report on the treatment of organic erectile dysfunction. J Urol 1996; 156: 2001-2007

Montorsi F, Kirby RS, Christiansen E et al. Long-term efficacy and tolerability of VIAGRA® in men with ED. Presented ESSIR, Rom 2001

Montorsi F, Salonia A, Zanoni M et al. Current status of local penile therapy. Int J Imp Research 2002; 14: Suppl 1, S70-S81

Moreland RB, Hsieh G, Nakane M et al. The biochemical and neurologic basis for the treatment of male erectile dysfunction. JPET 2001; 296: 225-234

Murthy KS. Activation of phosphodiesterase 5 and inhibition of guanylate cyclase by cGMP-dependent protein kinase in smooth muscle. Biochem J 2001; 360: 199-208

Nichols DJ, Muirhead GJ, Harness JA: Pharmacokinetics of Sildenafil citrate after single oral doses in healthy male subjects : absolute bioavailability, food effects and dose proportionality. Br J Clin Pharmacol 2002; 53: 5S-12S

NIH Consensus Statement of Impotence. Int J Impot Res 1993; 5: 181-199

Osterloh ICH. An update on Viagra. Presented at "Die Zukunft der ED-Behandlung", Hamburg, October 2001

Özdemir V, Kalow W, Bing-Kou T et al. Evaluation of the genetic component of variability in CYP3A4 activity: a repeated drug administration method. Pharmacogenetic 2000; 10: 373-388

Padma-Nathan H, McMurray JG, Pullman WE et al. On-demand IC351 enhances erectile function in patients with erectile dysfunction. IJIR 2001; 13: 2-9

Padma-Nathan H, Rosen RC, Shabsigh R et al. IC351 provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction (ED). Poster, presented at ESSIR, Rome 2001

Patterson B, Bedding A, Jewell H et al. Dose-normalized pharmacokinetic of Tadalafil (IC351) administered as a single dose to healthy volunteers. Poster, presented at ESSIR, Rome 2001

Patterson B, Bedding A, Jewell H et al. The effect of intrinsic and extrinsic factors on the pharmacokinetic properties of Tadalafil (IC351). Poster, presented at ESSIR, Rome 2001

Phillips S, Gbekor E, Bethell S et al. Selectivity of Sildenafil and other Phosphodiesterases Typ 5 (PDE5) inhibitors against all human phosphodiesterase families. Abstract presented at EAU, Birmingham 2002

Porst et al. Evaluation of Vardenafil, a new highly selective PDE5 inhibitor, in a double-blind, placebo-controlled study in 601 patients with erectile dysfunction. IJIR 2000; 12 (suppl): 22

Porst H, Buvat J, Lyklama AAB et al. Improved erectile function with Vardenafil throughout a 12-week study. ESSIR 2001

Porst H, Rosen R, Padma-Nathan H et al. Vardenafil, a new

highly selective PDE5 inhibitor, improves erectile function irrespective of the baseline severity and etiology of ED or age of patient. Poster, presented at EAU, Geneva 2001

Porst H, Rosen R, Padma-Nathan H et al. The efficacy and tolerability of Vardenafil, a new oral, selective PDE 5-I, in patients with ED: the first at home clinical trial, Int J Imp Res 2001; 13: 192-199

Porst H, Steidle C, Hollister A et al. Vardenafil demonstrated similar efficacy and tolerability among older and younger patients with marginal differences in PK characteristics between age groups. Poster, presented at ESSIR, Rome 2001

Porst H. Die tägliche oder bedarfsorientierte Verabreichung von IC351 zur Behandlung der erektilen Dysfunktion. Poster, presented at DGU, Hamburg 2000

Price D. Eine der häufigsten Ursachen für Erektionsstörungen: Diabetes mellitus. Der Urologe (B) 1999; 39 (6) (Suppl): 4

Pritzker MR. The penile stress test: A window to the hearts of man. Circulation 1999; 100 (Suppl): I-711

Rhode G, Wensing G, Unger S et al. The pharmacokinetics of Vardenafil, a new selective PDE 5 inhibitor, is minimally affected by coadministration with cimetidine or ranitidine. Pharmacotherapy 2001; Vol 21: No. 10

Roumegère T, Bollens R, Wespes E et al. Prevalence of hyperlipidemia and risk of coronary heart disease in a population with erectile dysfunction. J Urol 2001; Vol. 165: No. 5 (Suppl) 700

Sachs BD. Contextual approaches to the physiology and classification of erectile function, erectile dysfunction, and sexual arousal. Neursci and Biobehav 2000; Rev 24: 541-560

Sachse R, Rohde G. Safety, Tolerability and Pharmacokinetics of BAY 38-9456 in patients with erectile dysfunction. Poster, presented at AUA, Atlanta 2000

Sachse R, Rohde G. Safety, Tolerability and pharmacokinetics of multiple dose treatment with the new PDE5-inhibitor BAY 38-9456. Poster, presented at EAU, Brussels 2000

Sadovsky R, Miller T, Moskowitz M et al. Three-year update of Sildenafil citrate (Viagra) efficacy and safety. Int J Clin Pract 2001; 55: 115-128

Sáenz de Tejada I, Angulo J, Cuevas P et al. The phosphodiesterase inhibitory selectivity and the in vitro and in vivo potency of the new PDE 5 inhibitor vardenafil. Int J Imp Res 2001; 13: 282-290

Shakir SAW, Wilton LV, Boshier A et al. Cardiovascular events in users of Sildenafil : results from first phase of prescription event monitoring in England. BMJ 2001; 322: 651-652

Spector KR, Boyle M. The prevalence and perceived aetiology of male sexual problems in a non-clinical sample. Br J Med Psychol 1986; 59: 351–358

EU-SPC VIAGRA, Summary of Product Characteristics; Pfizer Inc. 2002

Steers W, Guay AT, Leriche A et al. Assessment of the efficacy and safety of VIAGRA® (sildenafil citrate) in men with erectile dysfunction during long-term treatment. Int J Impot Res 2001; 13: 261-267

Turko IV, Ballard SA, Francis SH et al. Inhibition of cyclic GMP-binding cyclic GMP-specific phosphodiesterase (typ5) by Sildenafil and related compounds. Mol Pharmacol 1999; 56: 124-130

Wallis RM, Leishman D, Pullman L et al. Effects of Sildenafil on retinal histopathology and electroretinogram (ERG) in dogs. Ophtalmic research 1998; (Suppl 1): 68 (341#).

Wespes E, Amar E, Hatzichristou D et al. Guidelines on Erectile Dysfunction. Europ Urol 2002; 41: 1-5

Wysowski DK, Farinas E, Swartz L. Comparison of Reported and Expected Deaths in Sildenafil (VIAGRA®) Users. Am J Cardiol 2002; Vol. 89

Yanaka N, Kotera J, Ohtsuka A et al. Expression, structure and chromosomal localization of the human cGMP-binding, cGMP-specific phosphodiesterase PDE5A gene. Eur J Biochem 1998; 255: 391-399

Zrenner E, Koppiker NP, Smith MD et al. The effects of long-term Sildenafil treatment on ocular safety in patients with erectile dysfunction (ED). Invest Ophtalmol Vis Sci 2000; 41: S 592 (# 3147)

Address for correspondance:
Professor Dr. med. Ursula Gresser
Praxisklinik Sauerlach
Internal Medicine
Tegernseer Landstr. 8
D-82054 Sauerlach, Germany
Phone: 0049-8104-88 78 22
Fax: 0049-8104-88 78 24
e-mail: info@praxisklinik-sauerlach.de

Professor Dr. med. Christoph Gleiter
Department of Clinical Pharmacology
University of Tübingen
Medizinische Klinik
Otfried-Müller-Str. 10
D-72076 Tübingen, Germany
Phone: 0049-7071-2 97 82 77
Fax: 0049-7071-29 50 35
e-mail: christoph.gleiter@uni-tuebingen.de