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Original Article

Sublingual sildenafil in the treatment of erectile dysfunction: Faster onset of action with less dose

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Abstract

Background: The aim of the present study was to show the efficacy and safety of sublingual sildenafil and to determine whether lower doses cause the same effect with a faster onset of action in this mode of application.

Methods: Fourty consecutive patients with erectile dysfunction for more than three months were included in the study. The mean age was 55 years (range, 25–65). Serum glucose and testosterone levels, lipid profile and erectile function scores were obtained in all patients. Twenty patients received placebos and the other 20 patients received 20 mg sublingual sildenafil in a double blind randomized design.

Results: The effect of sildenafil on erection was significantly higher than that of placebo. Sixty-five percent of patients (13/20) who received sublingual sildenafil achieved satisfying erections and coitus, whereas the rate was 15% in the placebo group (3/20). The mean onset of action with sublingual sildenafil was 15.5 min and lasted for an average of 40 min. Minimal headaches, sweating and flushing were noted as the side-effects.

Conclusions: 20 mg sublingual sildenafil is safe and effective in the treatment of erectile dysfunction. Sublingual administration has some advantages as it is not effected by food ingestion and quickly appears in the circulation. These advantages provide a faster onset of action with a lower dose when compared to oral sildenafil. Sublingual use of sildenafil may be more cost-effective and possibly provides a more predictable onset of action.

Key words erectile dysfunction, sildenafil, sublingual, treatment.

Introduction

Erectile dysfunction is a common problem that effects men of all ages and is defined as the inability to attain and maintain a satisfactory erection for sexual performance.[1] Previous studies have demonstrated that patients prefer oral medications to more invasive medical or surgical therapies for erectile dysfunction.[2] Sildenafil is a selective inhibitor of phosphodiesterase type 5 (PDE-5), that is, it inhibits cyclic guanosine monophosphate (cGMP) breakdown and therefore enhances the normal erectile response.[3]

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Since March 1998, after approval by the Food and Drug Administration, millions of men have tried oral sildenafil, leading to the accumulation of considerable data regarding its efficacy and side-effects. The onset of action with oral sildenafil citrate is within approximately 60 min in the presence of sexual stimulation.[3]

The present studyt was aimed at assessing the efficacy and safety of the sublingual form of sildenafil.

Materials and methods

Forty consecutive patients with erectile dysfunction were included in the present study. A detailed medical history was obtained and physical examination was performed, followed by laboratory tests, including the determination of serum glucose, lipid profile, testoster-

one and prolactine levels. Sexual function before and after treatment was objectively determined by the 5-item version of International Index of Erectile Function (IIEF-5).[4] The degree of severity of erectile dysfunction observed in patients was classified into five categories according to their IIEF-5 scores (Table 1). Success with treatment was defined according to IIEF-5 categories as 4 (mild ED) and 5 (no ED).

Patients were excluded from the study in the presence of any contraindication for sildenafil use, hormonal disorders, performance concern, unsteady sexual partnership, previous trial with oral sildenafil (patients who had previous experience with sildenafil) and chronic diseases, such as renal or hepatic failure. The patient profile with regard to risk factors is shown in Table 2.

The protocol was approved by the Institutional Review Board. After obtaining informed consent, the patients were randomized into two groups to receive either 20 milligrams of sublingual sildenafil (Durus SofTab, Durus Ltd, FL; $n = 20$) or placebo ($n = 20$) in a double-blind design**.** The formulation of Durus sofTab contains powdered sildenafil citrate, silica gel powder, sweeting solution, membrane transport enhancer and food coloring. All patients received the drug during sexual stimulation and they were asked to record the time between receiving the drug and onset of erection. Statistical analyses of data regarding time of onset and alterations in degree of severity of erectile dysfunction with placebo versus sublingual sildenafil were done by Wilcoxon-ranked sum and Mann-Whitney *U*-tests.

Table 1 Classification of the severity of erectile dysfunction according to the 5-item version of the International Index of Erectile Function

	Score	Category
Severe	5–7	1
Moderate	8–11	2
Mild to moderate	12–16	3
Mild	17–21	4
No erectile dysfunction	22–25	5

Table 2 Clinical characteristics of the patients included in the study ($n = 40$)

Charateristic	*n*
Mean age (years; range)	55 (25–65)
Risk factors	
Smoking (current and past smokers)	9
Diabetes mellitus	6
Hypertension	5
Benign prostatic hyperplasia	7
None	11
Patients having two or more risk factors	4

Results

The rate of achieving and maintaining erections for satisfactory intercourse were significantly higher in the sublingual group. Both placebo and sublingual sildenafil caused increases in IIEF-5 categories. While the mean increase in IIEF-5 categories after sublingual sildenafil was noted as 1.75 and statistically significant ($P = 0.02$), the corresponding mean rise in the placebo group was 0.6 and remained insignificant ($P > 0.05$). Accordingly, the mean post-treatment score in the sildenafil group was significantly higher than that in the placebo group ($P = 0.005$). The overall success rates were noted as 15% (3/20) in the placebo and 65% (13/20) in the sublingual sildenafil groups. Figure 1 shows the alterations in IIEF-5 categories with placebo and sublingual sildenafil.

The mean onset, that is, the time to achieve a rigid erection, was 15.5 min with sublingual sildenafil and 30 min with placebo. The effect of sublingual sildenafil for completed coitus lasted for an average of 40 min. The reported duration of effect was 20 min in the placebo group. Figure 2 shows the onset time of erections with placebo versus sublingual sildenafil.

The most common side-effects due to drug administration were headache (2/20 in sildenafil group and 1/20 in placebo group), flushing (2/20 in sildenafil group and 2/20 in placebo group) and sweating (2/20 in sildenafil group). All side-effects were minimal and well tolerated. All patients who achieved satisfactory erections and successful intercourses with sublingual sildenafil were eager to stay on this medication regularly.

Discussion

Even though Eardley and collegues report that oral sildenafil causes a penetrative erection in 12 min and for most patients within 30 min,[5] the consensus is that oral sildenafil effects after 60 min in the presence of sexual stimulation. Although available tablets are of 25, 50 and 100 mg, the suggested initial dose, regardless of the etiology of erectile dysfunction and anticipated side-effects, is 50 mg. Dose-response studies show that increased doses of sildenafil citrate cause an improvement in erectile function. After 24 weeks of treatment in a dose-response study, improved erections were reported in 56%, 77% and 84% for the men taking 25, 50 and 100 mg sildenafil, respectively.[3]

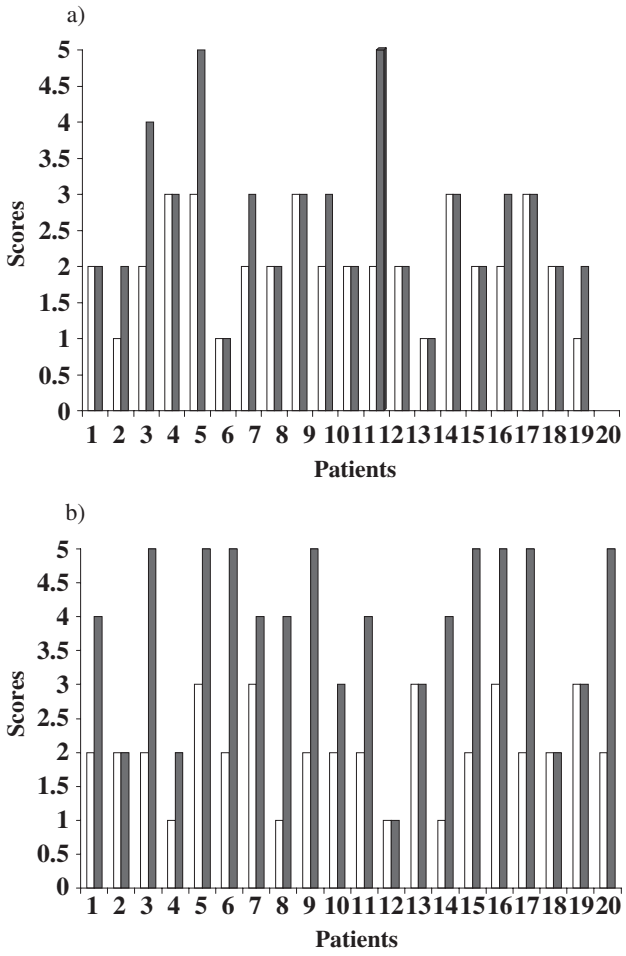

Fig. 1 (a) Alterations in the five-item version of the International Index of Erectile Dysfunction (IIEF-5) categories with placebo. (b) Alterations in IIEF-5 categories with sublingual sildenafil. □, pre-IIEF; ■, post-IIEF.

Oral sildenafil is metabolized predominantly by cytochrome p450 (CYP) 3A4 in the liver. CYP3A4 inhibitors, such as itraconazole, ketoconazole, clarithromycin, erythromycin, nefazodone, ritonavir and grapefruit juice result in reduced clearance of sildenafil.[6] The most common side-effects reported with oral sildenafil treatment are mild and transient headache, flushing, dyspepsia, nasal congestion and altered vision in color or brightness perception.[3] Although clinically significant hypotension is rare, it is contraindicated in patients who receive long-acting nitrates or who use short acting nitrate containing medications. Sildenafil must be used carefully within the six months after an acute myocardial infarction or stroke.[7] It is not recommended in patients with stable angina pectoris, uncontrolled hypertension or impaired cardiac reserve.[8]

The principal routes of sildenafil metabolism are N-demethylation, oxidation and aliphatic dehydroxylation.[9] The oraI administration of sildenafil has a limited bioavailbility due to first pass metabolism. In a previous study, the absolute bioavailability of oral administration was found to be 41%.[10] In another study that compared human pharmocokinetics and metabolism of single dose oral and intravenous sildenafil, the geometric mean area under the plasma concentration-time curve (AUC) between oral and intravenous administration routes had an absolute bioavailability of 38%. The total circulating fraction of sildenafil was 60% after intravenous and 32% after oral administration.[9] The bioavailability of a drug after sublingual administration may be similar to that after intravenous administration. Apparently, sublingual sildenafil will not be effected by digestion and will quickly appear in the circulation. These advantages provide a faster onset of action with a lower dose when compared to oral administration. The overall responses obtained in the presented series with 20 mg sublingual sildenafil was similar to that obtained with 50 mg oral sildenafil with less side-effects.[11]

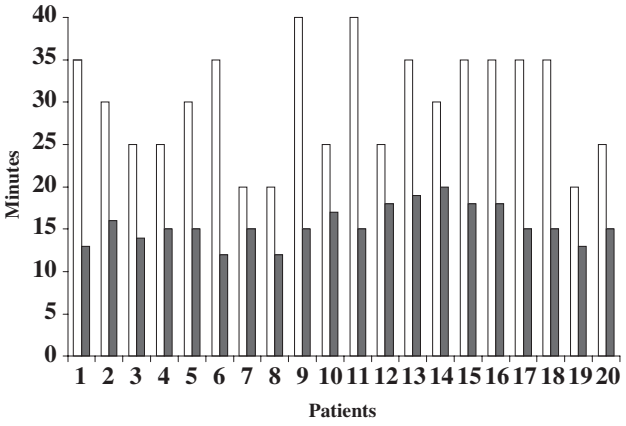

Fig. 2 Onset time of erections with placebo versus sublingual sildenafil. □, placebo; ■, sublingual sildenafil.

Sublingual sildenafil appears as an effective, safe and well tolerated agent for the treatment of erectile dysfunction. Obviously, pharmaco-galenic investigations and studies comparing the effect of oral sildenafil and sublingual sildenafil are needed, but these preliminary results obtained by using a different route of administration for this well-known agent are encouraging. Shorter onset of action with a smaller dose and fewer side-effects should be seriously considered in terms of cost-effectivity and better patient compliance.

References

1 National Institutes of Health. Consensus development panel on impotence. *JAMA* 1993; **280**: 83–90.

2 Jarow JP, Burnett AL, Geringer AM. Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment *J. Urol.* 1999; **162**: 722–5.
3 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil treatment erectile dysfunction. *N. Engl. J. Med.* 1998; **338**: 1397–404.
4 Rosen RC, Capelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int. J. Impot. Res.* 1999; **11**: 319–26.
5 Eardley I, Ellis P, Boolell M, Wulff M. Onset and duration of action of sildenafil for the treatment of erectile dysfunction. *Br. J. Clin. Pharmacol.* 2002; **53** (Suppl.): 61–5.
6 Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin. Pharmacokinet.* 2000; **38**: 41–57.
7 Lim PH, Moorthy P, Benton KG. The clinical safety of Viagra. *Ann. N. Y. Acad. Sci.* 2002; **962**: 378–88.
8 Cheitlin MD, Hutter AM Jr, Brindis RG, Kaul S, Russel RO Jr, Zusman RM. Use of sildenafil (Viagra) in patients with cardiovascular disease. *Circulation* 1999; **99**: 168–77.
9 Muirhead GJ, Rance DJ, Walker DK, Donald K, Wastall P. Comparative human pharmacokinetics and metabolism of single dose oral and intravenous sildenafil. *Br. J. Clin. Pharmacol.* 2002; **53** (Suppl.): 13–21.
10 Nichols DJ, Muirhead GJ, Harness JA. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects. Absolute bioavailability, food affects and dose proportionality. *Br. J. Clin. Pharmacol.* 2002; **53** (Suppl.): 55–63.
11 Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH. Clinical safety of oral sildenafil citrate (Viagra) in the treatment of erectile dysfunction. *Int. J. Impot. Res.* 1998; **10**: 69–74.

Appendix

The five-item version of the International Index of Erectile Dysfunction

Over the last 6 months, circle the number that most applies.

1 How do you rate your confidence that you could get and keep an erection?
1 Very low
2 Low
3 Moderate
4 High
5 Very high

2 When you had erections with sexual stimulation, how often were your erections hard enough for penetrarion?
1 Never or almost never
2 A few times (much less than half the time)
3 Sometimes (about half the time)
4 Most times (much more than half the time)
5 Almost always or always

3 During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
1 Never or almost never
2 A few times (much less than half the time)
3 Sometimes (*about* half the time)
4 Most times (much more than half the time)
5 Almost always or always

4 During sexual intercourse, how diffucult was it to maintain your erection to completion of intercourse?
1 Extremely difficult
2 Very difficult
3 Difficult
4 Slightly difficult
5 Not difficult

5 When you attempted sexual intercourse, how often was it satisfactory for you?
1 Never or almost never
2 A few times (much less than half the time)
3 Sometimes (about half the time)
4 Most times (much more than half the time)
5 Almost always or always