Evaluating erectile dysfunction: Oral sildenafil versus intracavernosal injection of papaverine

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ABSTRACT

Background. Intracavernosal injection of vasoactive drugs is an established method of evaluating erectile dysfunction. However, it is invasive and may be associated with pain and priapism. We investigated the use of oral sildenafil as a possible substitute for intracavernosal agents.

Methods. Men with erectile dysfunction were randomized into two groups of 25 each. One group of 25 men received injection papaverine initially followed by oral sildenafil, and another 25 received oral sildenafil followed by injection papaverine. Genital self-stimulation was used in both the groups. Penile length and circumference as well as angle of erection, before and after each medication, were recorded. Two days later, the intervention arms were crossed over. Subjective responses were obtained. The effect of medication on each outcome variable was studied by using analysis of variance models in relation to patient, period and medication.

Results. There was statistically significant improvement from the baseline value in both the arms, i.e injection papaverine and oral sildenafil ($p<0.001$, $p<0.001$, respectively) for both penile length and circumference. No significant difference was observed between the two medications in the outcome measures.

Conclusion. Oral sildenafil was as effective as injection papaverine in evaluating erectile dysfunction.

Natl Med J India 2005;18:299–301

INTRODUCTION

Erectile dysfunction (ED) is a common clinical problem affecting men of all ages.[1,2] Evaluation of ED was the terrain of psychotherapists before the 1980s. Since the introduction of papaverine in 1982 by Virag,[3] testing by intracavernosal injection of pharmacological agents became a well accepted procedure in the evaluation of ED.[4] While age is a definite risk factor for ED,[5] to our surprise, a majority of men attending our clinic are young and unmarried. We use intracavernosal agents routinely in these men to demonstrate their erectile power and, at the same time, to reassure them. However, injections are painful and associated with fear, anxiety, risk of extravasation and priapism.[6] Prostaglandins, though freely available, are expensive. Oral therapy is preferred to invasive medical or surgical therapies as demonstrated in studies done before the availability of oral drugs.[7,8] Sildenafil is an established oral therapy for ED.[9] It has also been shown to be useful as a second-line testing agent along with colour Doppler ultrasound (CDU).[10–12] We aimed to assess whether oral sildenafil was as useful as injectable papaverine in the evaluation of men with ED.

METHODS

Fifty men between 21 and 65 years of age who presented to our outpatient clinic at the Christian Medical College, Vellore, with a history of ED irrespective of aetiology, marital status and duration of ED were recruited for the study. Men in whom the use of either sildenafil or papaverine was contraindicated were excluded. All patients had at least a one month history of ED. A sexual function questionnaire was used to record the medical and sexual history. All patients underwent a detailed physical examination followed by focused vascular and neurological examinations. Biochemical investigations (lipid profile, serum testosterone, prolactin, follicle-stimulating hormone and luteinizing hormone) were done when indicated.

We used a cross-over study design. The sample size was calculated with 80% power of detecting a treatment benefit of 0.75 cm in length and the within-subject variance of the difference in mean length between the two periods of 3.34 cm, based on the two-

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TABLE I. Improvement in parameters in each medication arm as compared to the baseline

Outcome	Baseline	Papaverine	Baseline – papaverine (95% CI)	p value	Sildenafil	Baseline – sildenafil (95% CI)	p value
Length (cm)	7.71 (1.26)	11.98 (2.40)	–4.27 (–4.79 to –3.75)	0.001	11.66 (2.20)	–3.95 (–4.44 to –3.46)	<0.001
Circumference (cm)	7.50 (1.07)	10.02 (1.50)	–2.52 (–2.81 to –2.09)	0.001	9.67 (1.39)	–2.17 (–2.39 to –0.81)	<0.001

Values in parentheses are SD unless otherwise stated p value based on paired *t* test

TABLE II. Comparison of outcome between injection papaverine and oral sildenafil

Outcome*	Papaverine	Sildenafil	Difference (95% CI)	p value
Length (cm)	11.98 (2.10)	11.66 (2.14)	0.32 (–0.52 to 1.16)	0.45
Circumference (cm)	10.02 (1.34)	9.67 (1.30)	0.35 (–0.17 to 0.87)	0.19
Angle of erection	79.9 (18.89)	80.1 (17.87)	–0.20 (–7.49 to 7.09)	0.96

Values are mean (SD) unless otherwise stated *adjusted for subject, period and sequence effect using analysis of variance

sided test, with a significance level of 5% and also with an assumption of no carry-over effect.

Twenty-five subjects received injection papaverine initially followed by oral sildenafil and another 25 received oral sildenafil followed by injection papaverine, the order of medication being randomized by a computer programme. The two arms were separated by a wash-out period of 2 days. Injection papaverine 30 mg (intracavernosal) and sildenafil 50 mg (oral) were used in both the groups. All patients performed genital self-stimulation. Measurements were taken by the same observer 5 minutes after injection and 30 minutes after oral sildenafil. The dorsal length of the penis (from the symphysis pubis to the tip of the penis) and circumference (measured 1 cm proximal to the coronal sulcus) as well as its angle as described by Wespes *et al*.,[13] before and after each medication, were measured. Penile rigidity was evaluated by digital examination.

Patients were reviewed two hours after medication for evidence of priapism or untoward effects. The subjective response to and side-effects of medication were obtained. Improvement in parameters from the baseline in each medication arm was compared using a paired *t* test. The mean and standard deviation of outcome parameters between the two medication arms are presented. An analysis of variance model was also fitted, containing terms for the main effects of medication, period, carry-over, subject within sequence (order of randomization of medication).[14] The effect of carry-over was removed if it was non-significant at the 10% level; the main model which was then fitted included terms for subject, period and medication only.

RESULTS

Of the 50 men, 33 were married (66%), 16 were bachelors (32%) and one was divorced (2%). The mean (SD) age was 30 (10.2) years. Thirty had psychogenic impotence and 20 had some contributing medical conditions (6 had diabetes mellitus, 3 had hypertension, 2 abused alcohol, 4 had a depressive illness and were on medication, 3 had anxiety neurosis and 1 each had cerebrovascular accident and neuropathy).

The mean (SD) penile length was 7.71 (1.26) cm at baseline, but improved in the papaverine arm by 4.27 cm (11.98 [2.40] cm) and in the sildenafil arm by 3.95 cm (11.66 [2.20] cm). The difference in penile length was significant in both the arms ($p<0.001$, $p<0.001$ respectively; Table I). The mean penile circumference was 7.50 (1.07) cm at baseline and improved with papaverine by 2.52 cm (10.02 [1.5] cm) and with sildenafil by 2.17 cm (9.67 [1.39] cm). There was a statistically significant improvement with both the medications compared with the baseline penile circumference ($p<0.001$, $p<0.001$, respectively; Table I).

After adjusting for the subject, period and sequence effects, the outcome between the two arms was compared (Table II). The improvement in outcome variables, i.e length, circumference and angle of erection was similar with papaverine and sildenafil (p values 0.45, 0.19, 0.96, respectively).

Subjective parameters, when analysed, showed that 20 of the 50 men (40%) favoured the oral drug over injection, compared with 24 men (48%) who favoured the injection. Three men (6%) scored equally for both the medications and 3 (6%) had no response to either. Five men had priapism (10%) following injection; of them, 3 required a corporal wash. Following sildenafil, 2 had headache (4%), 1 had blurring of vision (2%) and 1 had dyspepsia (2%).

DISCUSSION

The 1993 National Institutes of Health (NIH) Consensus Panel[1] defined ED, a relatively common problem affecting men of all ages, as 'the inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity'. In the Massachusetts Male Aging Study (MMAS),[2] 52% of subjects had some degree of ED and 35% of men aged 40–70 years reported moderate to complete impotence. ED was found to be an age-dependent disorder with a prevalence ranging from 0.1% at 20 years of age to 75% at 80 years.[15] Invasive and non-invasive methods have been used to understand the mechanism of erection and its alteration in illness. Nocturnal penile tumescence (NPT) was considered the first diagnostic test in the impotent male and is based on the change in penile diameter during sleep.[16] The device to measure this is sophisticated, expensive, requires at least 2 nights in a sleep laboratory and includes polysomnographic monitoring to rule out a sleep disorder.[17] The NPT methodology has been criticized because of its failure to include adequate measurements of both circumference and rigidity.[18]

Pharmacological testing agents not only indicate the presence or absence of organic conditions, but are also predictors of the therapeutic response. The ideal agent for pharmacological testing should be one that will cause full but not prolonged erection. Unfortunately, there is no ideal drug available, nor are the criteria for erectile response defined.[19] Papaverine and prostaglandins have been used extensively, but are associated with side-effects such as priapism, pain and ecchymosis. Audiovisual sexual stimulation (AVSS) has been used to distinguish between organic and psychogenic causes of ED. Slob *et al*.[20] reported the use of AVSS

in conjunction with NPT and an erectiometer, and concluded that it may be useful as an initial screening test.

A literature review revealed inconsistent data regarding the erectogenic capacity of AVSS without pharmacological testing agents. Cahill *et al*.[21] were unable to obtain any meaningful response in 25 patients and Fouda *et al.*[22] found a positive response to AVSS alone in 6.6% of their patients. Moreover, AVSS does not usually result in ejaculation and some patients may have a cultural or moral aversion to pornography.[23]

Genital stimulation is usually involved in foreplay and is more physiological.[23] The main argument against the use of sildenafil in the experimental setting was the lack of sexual stimulation. We use tactile stimulation routinely in our clinic along with intracavernosal injections. We decided to test this hypothesis in addition to assessing objectively the role of sildenafil in the evaluation of ED. Rigiscan, rigidometer and snap gauge can be used to evaluate rigidity but such equipment adds to the cost of evaluation.[24]

We found that oral sildenafil is as effective as papaverine. The subjective and objective responses were highly corroborative. Though the onset of erections was delayed, their duration and quality were comparable. Adverse effects were seen in only 8% of men; all these effects were mild and none of the men had priapism. The response in men who had had no prior sexual encounter was also favourable.

In summary, oral sildenafil was as effective as injection papaverine in evaluating ED. We recommend the use of oral sildenafil with genital self-stimulation as an office procedure in the evaluation of ED, especially in young men with psychogenic impotence.

ACKNOWLEDGEMENTS

We thank Mr Samson, male nurse, for his assistance in maintaining the records and Mr Ramesh, our secretary, for help in preparing this manuscript.

REFERENCES

1 NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA* 1993;**270:**83–90.
2 Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. *J Urol* 1994;**151:**54–61.
3 Virag R. Intracavernous injection of papaverine for erectile failure. *Lancet* 1982;**2:**938.
4 Brindley GS. Cavernosal alpha-blockade: A new technique for investigating and treating erectile impotence. *Br J Psychiatry* 1983;**143:**332–7.
5 Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: Prevalence and predictors. *JAMA* 1999;**281:**537–44.
6 Linet OI, Ogrinc FG. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. *N Engl J Med* 1996;**334:**873–7.
7 Jarow JP, Nana-Sinkam P, Sabbagh M, Eskew A. Outcome analysis of goal directed therapy for impotence. *J Urol* 1996;**155:**1609–12.
8 Lue TF. Impotence: A patient's goal-directed approach to treatment. *World J Urol* 1990;**8:**67–74.
9 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.
10 Bacar MM, Batislam E, Altinok D, Yilmaz E, Bacar H. Sildenafil citrate for penile hemodynamic determination: An alternative to intracavernosal agents in Doppler ultrasound evaluation of erectile dysfunction. *Urology* 2001;**57:**623–6.
11 Arslan D, Esen AA, Secil M, Aslan G, Celebi I, Dicle O. A new method for the evaluation of erectile dysfunction: Sildenafil plus Doppler ultrasonography. *J Urol* 2001;**166:**181–4.
12 Erdogru T, Usta MF, Ceken K, Koksal T, Ates M, Kabaalioglu A, *et al.* Is sildenafil citrate an alternative agent in the evaluation of penile vascular system with color Doppler ultrasound? *Urol Int* 2002;**68:**255–60.
13 Wespes E, Delcour C, Rondeux C, Struyven J, Schulman CC. The erectile angle: Objective criterion to evaluate the papaverine test in impotence. *J Urol* 1987;**138:** 1171–3.
14 Jones B, Kenward MG. *Design and analysis of cross over trials.* London:Chapman and Hall; 1989:22–32.
15 Kinsey AC, Pomeroy WB, Martin CF. *Sexual behaviour in the human male.* Philadelphia:WB Saunders; 1948.
16 Wasserman MD, Pollak CP, Spielman AJ, Weitzman ED. The differential diagnosis of impotence. The measurement of nocturnal penile tumescence. *JAMA* 1980;**243:** 2038–42.
17 Meisler AW, Carey MP. A critical reevaluation of nocturnal penile tumescence monitoring in the diagnosis of erectile dysfunction. *J Nerv Ment Dis* 1990;**178:**78–89.
18 Wein AJ, Fishkin R, Carpiniello VL, Malloy TR. Expansion without significant rigidity during nocturnal penile tumescence testing: A potential source of misinterpretation. *J Urol* 1981;**126:**343–4.
19 Meuleman EJ, Bemelmans BL, Doesburg WH, van Asten WN, Skotnicki SH, Debruyne FM. Penile pharmacological duplex ultrasonography: A dose–effect study comparing papaverine, papaverine/phentolamine and prostaglandin E1. *J Urol* 1992;**148:**63–6.
20 Slob AK, Blom JH, van der Werff ten Bosch JJ. Erection problems in medical practice: Differential diagnosis with a relatively simple method. *J Urol* 1990;**143:**46–50.
21 Cahill BE, Ross EV, Pielet RW, Rice JC, Lewis RW, Kerstein MD. Measurement of impotence by laser Doppler flowmetry and conventional methodology. *J Urol* 1988;**140:**749–50.
22 Fouda A, Hassouna M, Beddoe E, Kalogeropoulos D, Binik YM, Elhilali MM. Priapism: An avoidable complication of pharmacologically induced erection. *J Urol* 1989;**142:**995–7.
23 Donatucci CF, Lue TF. The combined intracavernous injection and stimulation test: Diagnostic accuracy. *J Urol* 1992;**148:**61–2.
24 Maatman TJ, Montague DK, Martin LM. Cost-effective evaluation of impotence. *Urology* 1986;**27:**132–5.