Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson’s disease or multiple system atrophy with observations on orthostatic hypotension

I F Hussain, C M Brady, M J Swinn, C J Mathias, C J Fowler

Abstract

Objectives—To assess the efficacy and safety of sildenafil citrate (Viagra) in men with erectile dysfunction and parkinsonism due either to Parkinson’s disease or multiple system atrophy.

Methods—Twenty four patients with erectile disease were recruited, 12 with Parkinson’s disease and 12 with multiple system atrophy, into a randomised, double blind, placebo controlled, crossover study of sildenafil citrate. The starting dose was 50 mg active or placebo medication with the opportunity for dose adjustment depending on efficacy and tolerability. The international index of erectile function questionnaire (IIEF) was used to assess treatment efficacy and a quality of life questionnaire to assess the effect of treatment on sex life and whole life. Criteria for entry included a definite neurological diagnosis and a standing systolic blood pressure of 90–180 mm Hg and diastolic blood pressure of 50–110 mm Hg, on treatment if necessary. Blood pressure was taken at randomisation (visit 2) and crossover (visit 5) lying, sitting, and standing, before and 1 hour after taking the study medication in hospital.

Results—Sildenafil citrate was efficacious in men with parkinsonism with a significant improvement, as demonstrated in questionnaire responses, in ability to achieve and maintain an erection and improvement in quality of sex life. In Parkinson’s disease there was minimal change in blood pressure between active and placebo medication. In multiple system atrophy, six patients were studied before recruitment was stopped because three men showed a severe drop in blood pressure 1 hour after taking the active medication. Two were already known to have orthostatic hypotension and were receiving treatment with ephedrine and midodrine but the third had asymptomatic hypotension. However, the blood pressures in all three had been within the inclusion criterion for the study protocol. Despite a significant postural fall in blood pressure after sildenafil, all patients with multiple system atrophy reported a good erectile response and were reluctant to discontinue the medication.

Conclusions—Sildenafil citrate (50 mg) is efficacious in the treatment of erectile dysfunction in parkinsonism due to Parkinson’s disease or multiple system atrophy, however, it may unmask or exacerbate hypotension in multiple system atrophy. As Parkinson’s disease may be diagnostically difficult to distinguish from multiple system atrophy, especially in the early stages, we recommend measurement of lying and standing blood pressure before prescribing sildenafil to men with parkinsonism. Furthermore, such patients should be made aware of seeking medical advice if they develop symptoms on treatment suggestive of orthostatic hypotension.

Keywords: erectile dysfunction; Parkinson’s disease; multiple system atrophy; viagra; orthostatic hypotension
system atrophy, autonomic symptoms, including erectile dysfunction, were the initial features of the disease in 41% and had subsequently developed in 97% of male patients; symptomatic orthostatic hypotension, although present in 68%, was severe and caused fainting in only 15% of patients.7 The symptoms caused by orthostatic hypotension have been studied in 40 patients with multiple system atrophy, and despite an orthostatic blood pressure fall of >30 mm Hg less than 50% have syncope (unlike pure autonomic failure), whereas others only have symptoms such as fatigue, lethargy, and weakness.8

The extensive clinical database that already exists for sildenafil citrate demonstrates that it is efficacious in the management of erectile dysfunction, and safe when appropriately used. The contraindication with any form of nitrate therapy is absolute because a synergistic response can result in severe hypotension.9 In normal volunteer studies sildenafil reduced mean maximum supine systolic and diastolic blood pressure by about 8 mm Hg and 5 mm Hg without an effect on the heart rate.

The safety and efficacy of sildenafil for the treatment of erectile dysfunction in Parkinsonism due to Parkinson’s disease and multiple system atrophy had not been studied before. Although multiple system atrophy is less common than Parkinson’s disease, it is a disease in which most men have erectile dysfunction and because orthostatic hypotension may be a complication, such a study is of particular relevance.

Methods

PATIENTS

Twenty-four male patients with a well-documented history of erectile dysfunction, 12 with a diagnosis of Parkinson’s disease, and 12 with multiple system atrophy had not been studied before. Patients with diabetes, retinitis pigmentosa, a history of alcohol or drug dependence, and sex life. Responses range from 0 to 5 (very dissatisfying to very satisfying).

The patient’s partner was also given a brief questionnaire to complete independently. The primary efficacy end points were the responses to questions 3 and 4 of the IIEF and responses to the QoL questionnaire.

TRIAL DESIGN

The trial was designed as a randomised, double blind, placebo controlled, crossover study with flexible dosage starting at 50 mg active medication or placebo and was conducted over a 24 week period in each patient. The dose could be titrated up to 100 mg or down to 25 mg depending on efficacy and tolerability. Medication was on an “as needed” basis 1 hour before sexual activity and patients were provided with three tablets a week but advised not to take more than one each day.

At visit 1, consent was obtained before demographic data and screening blood samples were taken. Patients were advised to stop all therapy for erectile dysfunction and sexual activity was encouraged. After a 4 week run in period (visit 2), patients filled in a baseline IIEF questionnaire and were randomised to receive either 50 mg sildenafil citrate or placebo medication. The first dose was taken in the department and the heart rate with lying, sitting and standing blood pressures were recorded before and 1 hour after dosing. At visits 3 and 4 the dose was titrated up or down if necessary, depending on efficacy and tolerability. At visit 5, after 10 weeks of treatment, patients attended for the crossover and the same procedure was repeated, visits 6 and 7 being similar to visits 3 and 4. At the final visit, the patients repeated the IIEF questionnaire and had a further blood test.

Medication was kept in the pharmacy together with the randomisation detail and only enough was dispensed until the next visit. Patients were required to keep a dosing log.

Statistical analysis was carried out by Pfizer, New York, USA. A crossover analysis of variance (ANOVA) model was utilised with terms for sequence, patient, period, and
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Patients with multiple system atrophy who tolerated the medication with minimal effect on their blood pressures (top panel); three patients who developed a symptomatic fall in their blood pressures 1 hour after treatment with sildenafil (bottom panel).

**Results**

**Parkinson's Disease**

Of the 12 men with Parkinson's disease recruited, 10 completed the study, one withdrew consent at visit 3 and another was found to have carcinoma of the lung during the run-in period and was not treated. Four of 10 patients were randomised to receive the placebo for the first 10 weeks and the remainder for the second 10 weeks. Nine of 10 patients reported a good response to sildenafil citrate, eight titrated up to 100 mg and one titrated down to 25 mg. One patient reported lack of efficacy and returned to intracavernosal injections at the conclusion of the study.

Overall the baseline and 10 week postplacebo data for IIEF (questions 3 and 4) and the QoL for whole life and sex life were similar.

**Discussion**

We have shown that sildenafil citrate is efficacious in the treatment of erectile dysfunction in patients with parkinsonism having Parkinson's disease or multiple system atrophy.
Sildenafil enhanced erectile function, enabling intercourse, which resulted in an improved quality of sex life. It was well tolerated in Parkinson’s disease and the minor adverse effects of headache and flushing were transient and required no treatment. However, in multiple system atrophy, sildenafil caused a severe fall in blood pressure in half of the treated patients, resulting in early termination of the study. The adverse event was recognised because the first dose of all medication was taken under supervision in the department. Two of these patients were already receiving treatment with ephedrine and midodrine for orthostatic hypotension and all three patients with this adverse event had a significant fall in postural blood pressure before sildenafil, which potentiated the response. However, on treatment their lying, sitting, and standing blood pressures were within the inclusion criteria for the study protocol. Despite severe and symptomatic hypotension, all three wanted to continue to use the medication and were dismissive of the suggestion that sildenafil was unsafe for them. One patient obtained it via the internet although he was made aware of the possible hazards. The three men with multiple system atrophy who tolerated the medication well had minimal postural fall in blood pressure and although the lying, sitting, and standing pressures were lower with active medication there was no postural accentuation (fig 1). Thus, the presence of orthostatic hypotension and its magnitude was predictive of a further fall and adverse reaction to sildenafil.

Debate continues about the mechanisms causing erectile dysfunction in multiple system atrophy, and a mechanism which includes impairment of dopaminergic mediated pathways in the CNS—which are being increasingly recognised as important for erectile function—should be considered. The demonstrated efficacy of sildenafil in the presence of orthostatic hypotension indicates that hypotension itself, with reduced filling pressures, cannot be causal. There are often difficulties in early diagnosis and separation of Parkinson’s disease from multiple system atrophy. Although orthostatic hypotension is uncommon in early Parkinson’s disease, this is not the case in multiple system atrophy. We recommend measurement of lying and standing blood pressure before prescribing sildenafil to men with parkinsonism. Furthermore, such men should be followed up with blood pressure measurements and made aware of the need to seek medical advice if they develop symptoms suggesting orthostatic hypotension.

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