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Original Article

Early experience with sildenafil for the treatment of erectile dysfunction in renal transplant recipients

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Abstract

Background. Erectile dysfunction (ED) is common in men with renal failure, but is not always alleviated following kidney transplant. The objective of the present study was to assess the feasibility in renal transplant patients of sildenafil citrate treatment, an agent with proven efficacy in the management of ED.

Methods. This was a phase IV, open, multicentre, 3 month, dose-escalation study. All patients meeting the inclusion criteria were prescribed a dose of 50 mg sildenafil at the first visit. Thereafter the dose could be increased to 100 mg or reduced to 25 mg based on efficacy or tolerability. The primary efficacy parameter assessed the ability of patients to achieve erections sufficient for intercourse and to maintain erections after penetration. Secondary endpoints assessed patient satisfaction with sildenafil and the effect of sildenafil on their quality of life. Patients were carefully monitored throughout the study for adverse events, interactions with immunosuppressive therapy and effect on graft function.

Results. The study included 50 patients in the intent-to-treat population. Sildenafil significantly improved patient's erection ability and the frequency of their erection maintenance. Analysis of the secondary efficacy parameters revealed that 66% of patients believed treatment had improved their erections. Patients reported improvements in their sexual life and partner relationships and a high level of satisfaction with treatment. There were no interactions between sildenafil and the immunosuppressive drugs and there was no significant adverse effect of sildenafil on graft function.

Conclusions. Sildenafil is an effective and well-tolerated agent for the treatment of ED in renal transplant recipients.

Keywords: erectile dysfunction; quality of life; renal transplant; sildenafil

Introduction

The ability of patients to regain a normal quality of life following renal transplant has increased significantly in the past decade with improvements in transplant procedures and graft survival. However, one area where significant improvements have not been made is in the ability of patients to fulfil sexual relationships with their partner. Erectile dysfunction (ED) remains a problem for many patients post-transplant.

ED is defined as the inability to attain and maintain an erection sufficient to allow satisfactory sexual intercourse [1]. Surveys conducted in the general population suggest it is a common condition, affecting ~50% of men aged 40–70 years to some degree and increases in frequency with age [2,3]. Among patients with chronic renal failure the prevalence of ED is even higher with estimates ranging from 40 to 75% [4–6].

ED in men with chronic renal failure cannot be attributed to one single cause, but rather to multiple organic and psychological factors. Organic factors include neuroendocrine disturbances, uraemia, vascular insufficiency, venous incompetence and associated chronic diseases (i.e. hypertension, diabetes mellitus, atherosclerosis) [7]. Neuroendocrine disturbances are often reversed by renal transplantation, but not by dialysis. Psychological factors may also contribute to ED in renal failure patients. It has been reported that

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approximately one-quarter of renal dialysis patients are depressed at any given time [8]. As a result of the many co-morbid conditions, renal failure patients may also be taking a number of concomitant medications that may themselves predispose patients to ED.

The ED present in uraemic (pre-dialysis) and dialysis patients is alleviated in a number of individuals after transplantation, but in other cases erectile function may be adversely affected. An evaluation of erectile function in renal transplant recipients found that of 65 patients, 32 (49.2%) experienced no alteration in erectile function before or after renal transplantation, 12 patients (18.4%) regained erectile function and 21 patients (32.3%) with normal erectile function before transplantation reported ED after the transplant [9]. In another study, Malavaud *et al.* [10] evaluated male sexual function in 271 kidney transplant recipients using the International Index of Erectile Function. The study found that of 212 sexually active patients, 55.7% were suffering from ED.

A number of treatment options are available for patients with ED. Sildenafil citrate is the first oral therapy with proven efficacy in men with ED of a broad spectrum of aetiology, including those with concomitant medical conditions such as hypertension, history of pelvic surgery, diabetes mellitus and ischaemic heart disease. In all these patients, sildenafil has been shown to significantly improve patients' abilities to achieve and maintain an erection compared with placebo [11–13]. Until now, sildenafil has not been evaluated in renal transplant recipients with ED. However, in renal dialysis patients, preliminary observations, albeit in small numbers of patients, showed that 66–80% of patients believed that sildenafil treatment had improved their erections [14,15].

There is clearly a need for an effective oral therapy to manage ED in patients post-transplant. Such a therapy would need to be safe for co-administration with immunosuppressive drugs and have no effect on grafted tissue. The objective of the present study was therefore to assess the feasibility of treatment with sildenafil in a renal transplant population. It is a sub study of a larger trial designed to assess the efficacy of sildenafil in patients with ED by its effect on patient quality of life.

Subjects and methods

Patients

Male renal transplant recipients with a clinical diagnosis of ED, defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance [1] were included in the study. Patients were aged 18 years or older and were in a stable relationship (according to the patient and investigator's estimation).

Patients were excluded if they had genital anatomical deformities that would have significantly impaired erection; had a coexisting sexual disorder in addition to ED; had serum creatinine levels >180 μmol/l and/or transplantation <6 months previously; experienced any change in the administration of medication known to be causally associated with ED (e.g. beta blockers, tricyclic antidepressants); were prescribed nitrate derivatives and nitric oxide donors in any form; were not prepared to discontinue use of other devices or treatments for ED for the duration of the study; and received an experimental drug within the past 3 months.

The protocol was approved by an Independent Ethics Committee and every patient provided witnessed, written, informed consent prior to entering the study.

Study design

This was a phase IV, open, multicentre, flexible, dose-escalation, 3 month treatment study. Following inclusion, patients had to return to the clinic for follow-up visits after 2, 6 and 12 weeks of treatment to provide assessments of efficacy, safety and drug accountability. At week 0 (start of treatment) and week 12 (end of the study), patients completed a number of efficacy assessment questionnaires. Patients were also required to record the actual date of dosing and the number of tablets taken.

Dosing

Sildenafil citrate was available as 25, 50 and 100 mg tablets. Patients were instructed to take a dose when required for sexual activity, but not more than once daily. The tablet had to be taken $\sim$1 h prior to sexual activity. All patients were prescribed a dose of 50 mg sildenafil at visit 1 to be taken during the first 2 weeks of the study. At visit 2, patients in whom the 50 mg dose was well tolerated, but whose ED was not sufficiently improved could have their dose increased to 100 mg. Lack of improvement had to be based on a minimum of two attempts at sexual activity following sexual stimulation. Patients who responded well at a particular dose were not allowed to receive higher doses. Patients who were on the 50 or 100 mg dose were allowed to decrease their dose to the next lowest level (25 or 50 mg, respectively) only if they were experiencing intolerable side effects.

Efficacy parameters

Efficacy parameters were measured using four assessment instruments. The primary measure was a sexual function questionnaire, the International Index of Erectile Function (IIEF), which was completed at baseline and again at the end of the study. The IIEF questionnaire is specifically developed to assess the sexual function of patients suffering from ED. Two of the questions from the IIEF served as primary study endpoints: (i) the ability to achieve erections sufficient for sexual intercourse and (ii) the maintenance of erections after penetration. Secondary endpoints included information gained from the IIEF about other aspects of sexual function, such as information on erectile function, orgasm, desire, satisfaction with intercourse and overall satisfaction. Secondary endpoints were also evaluated by three other assessment instruments. The quality of life index-life satisfaction check-list (LISAT) assessed patient satisfaction with different domains of life. The Global Efficacy Questionnaire and the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) assessed the patient's satisfaction with treatment.

Safety evaluation

Before entering the study and at the end of treatment patients underwent a complete physical examination. Sitting blood

pressure (BP) and heart rate were recorded at each visit. Clinical laboratory evaluations included serum creatinine levels and trough blood levels of immunosuppressive drug. For patients that had both renal and pancreatic transplants, additional laboratory evaluations included levels of fasting blood sugar, post-prandial blood sugar and glycated haemoglobin. At each visit the investigator had to obtain any information about concurrent illness and any therapeutic interventions (e.g. drug therapy, surgery). All observed or volunteered adverse events regardless suspected causal relationship to study drug were recorded. These included events involving adverse drug reactions, illnesses commencing during the study or exacerbation of pre-existing illnesses. A serious adverse event was defined as any adverse drug experience occurring at any dose that: resulted in death, was life-threatening, resulted in in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or congenital anomaly/birth defect.

Laboratory analyses

All clinically important abnormal laboratory tests occurring during the study had to be repeated at appropriate intervals until they returned either to baseline or to a level deemed acceptable by the investigator, or until a diagnosis that satisfactorily explained them was made.

Statistical analysis

The intent-to-treat population was composed of all renal transplant patients included (including those who had received renal and pancreatic transplants), who had taken the treatment at least once during the study and for whom primary endpoint data, questions 3 and 4 of the IIEF, were collected at baseline. The per protocol population was composed of all renal transplant patients included in the study who had taken treatment at least once, who completed the study (visits V1 and V4 performed), and who completed questions 3 and 4 of the IIEF at baseline and V4 with no major protocol deviation. The safety population was composed of all those who had taken the treatment at least once during the study.

For the main efficacy parameters, the level of significance was fixed at 2.5%. For the secondary endpoints, the level of significance was fixed at 5%. The evolution of the answers to questions 3 and 4 of the IIEF between week 0 and week 12 was described and compared with 0 using a non-parametric Wilcoxon Sign Rank test. In addition, answers between week 0 and week 12 were compared according to presence or not of a dialysis, the duration of the dialysis and the duration of the last transplantation. For the General Efficacy Questionnaire a logistic regression was performed according to the following variables: age, answer to question 3 of the IIEF at the end of the study, answer to question 4 of the IIEF at the end of the study, rate of successful intercourse at the end of the study, cause of the ED, onset of the ED, presence of nocturnal erections, presence or not of a dialysis, duration of the dialysis and the duration of the last transplantation.

Results

Patients

The renal transplant population consisted of 54 individuals from eight centres. The efficacy analysis was performed on two populations: the intent-to-treat population ($n=50$) and the per protocol population ($n=43$). Results were similar for both populations and only those of the intent-to-treat population are presented in this report.

Overall, 11 patients (20.4%) discontinued the study prematurely: four patients had an insufficient clinical response, two patients were withdrawn due to an adverse event, three patients did not meet the entry criteria, one patient withdrew his consent, and one patient was not considered compliant because his depressive condition deteriorated. The response quality of the questionnaires was good indicating that they were well accepted by the patients. For the IIEF, 46 out of 52 (88.5%) questionnaires were completed without missing data at visit 1 and 44 out of 46 (95.6%) at visit 4, or time of discontinuation.

Baseline characteristics for the total renal transplant population are illustrated in Table 1. Characteristics of the per protocol population are similar to those of the total population and are not presented here. The mean age was 54 ± 9 years. The most common existing medical conditions were hypertension (90.7%), diabetes (29.6%), coronary insufficiency (9.3%) and depression (3.7%). On average, systolic BP was 138.7 ± 13.2 mmHg, diastolic BP was 81.3 ± 7.9 mmHg and

Table 1. Baseline characteristics of intent-to-treat population

	Number (%)
Mean age ± SD (years)	54.1 ± 9.0
Race	
Caucasian	50 (92.6)
Black	4 (7.4)
Tobacco consumption	
Yes	7 (13.0)
No	47 (87.0)
Alcohol consumption	
Yes	30 (55.5)
No	24 (44.4)
Medical history	
Current depression	2 (3.7)
Hypertension	49 (90.7)
Diabetes mellitus	16 (29.6)
Coronary insufficiency	5 (9.3)
Transplant history	
Mean age of transplant ± SD (months)	66.6 ± 61.2
Kidney transplant	49 (90.7)
Kidney + pancreatic transplant	5 (9.3)
Initial nephropathy	
Non-diabetic glomerulopathy	25 (46.3)
Diabetic glomerulopathy	8 (14.8)
Chronic interstitial nephropathy	5 (9.3)
Nephro-angiosclerosis	2 (3.7)
Polycystic disease	6 (11.1)
Non-determined nephropathy	8 (14.8)
Type of dialysis	
Haemodialysis	46 (85.2)
Peritoneal dialysis	4 (7.4)
Pre-emptive transplant	4 (7.4)
Mean duration of dialysis ± SD (months)	113.7 ± 82.4
Number of previous transplants	
0	46 (85.2)
1	7 (13.0)
2	1 (1.8)

Table 2. ED history of the total population of renal transplant patients

	Number (%)
Mean duration of ED ± SD (years)	6.8 ± 5.9
Cause of ED	
Psychogenic	1 (1.8)
Organic	14 (26.0)
Mixed (psychogenic + organic)	39 (72.2)
Onset of ED	
Progressive	44 (81.5)
Sudden	10 (18.5)
Nocturnal erections	
Yes	26 (48.1)
No	25 (46.3)
Unknown	3 (5.6)
Previous treatment of ED	
Yes	11 (20.4)
No	43 (79.6)

the pulse rate was 71.4 ± 10.4 b.p.m. Mean serum creatinine levels were 138.0 ± 35.8 μmol/l. The trough blood levels of immunosuppressive treatment were 9.30 ± 3.44 for tacrolimus ($n = 9$) and 133.15 ± 88.22 for cyclosporine ($n = 40$).

The average duration of kidney transplant was 66.6 ± 61.2 months, of which 9% were kidney–pancreas transplants and 91% were kidney only. In the majority of patients (92.6%) the transplant(s) came from a brain-dead donor. The initial nephropathy was a non-diabetic glomerulopathy in 46.3% of cases. The majority of patients (85.2%) had had haemodialysis and the average length of the dialysis had been 113.7 ± 82.4 months. Most of the 54 patients included (85.2%) had not had a previous transplant; 13% of the patients had had one previous transplant and 1.8% had had two previous transplants. In only one patient had both internal iliac arteries been used as a blood supply for his two transplants, possibly decreasing necessary blood flow to the penis.

On average the duration of ED was 6.9 ± 5.9 years (Table 2). In 39 patients (72.2%) the cause of the ED was mixed. The cause was organic in 14 patients (26%) and psychogenic in one patient (1.8%). Overall, 48.2% of the patients had nocturnal erections. For 11 of the 54 patients (20.4%), at least one previous drug treatment of ED was noted. The treatments reported by the investigator were: sildenafil, alprostadil, tianeptine, tamsulosine, ifenprodil, yohimbine, naftidrofuryl and thymoxamine.

At the end of the study, 27 patients (53%) were taking a dose of 100 mg/day, one patient (2%) was taking a dose of 75 mg/day, 22 patients (43%) were taking a dose of 50 mg/day and one patient (2%) was taking a dose of 25 mg/day. The average number of tablets taken per week between inclusion and the end of the study was 3.3 ± 1.7 tablets.

Efficacy

Primary efficacy parameters. Patients' responses to questions 3 and 4 of the IIEF are illustrated in Table 3 for the intent-to-treat population. For question 3 (over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate your partner?) pre-treatment score (1.9 ± 1.6) was statistically different from the post-transplant score (3.2 ± 1.8, $P < 0.0001$). Fifty-eight per cent of patients answered 'sometimes', 'a few times' or 'almost never or never' at visit V1. At the final visit, 54% of patients answered 'almost always or always' or 'most times.'

Patient's responses to question 4 (over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?) were also significantly improved compared with baseline. Pre-treatment score (1.8 ± 1.5)

Table 3. Response to questions 3 and 4 of the IIEF for the intent-to-treat population

	Number (%) of patients	
	Visit 1 ($n = 50$)	Visit 4 ($n = 50$)
Answer to question 3 of the IIEF regarding the 'erection ability'		
Not concerned	11 (22)	7 (14)
Almost never or never	15 (30)	5 (10)
A few times (much less than half the time)	5 (10)	2 (4)
Sometimes (about half the time)	9 (18)	9 (18)
Most times (much more than half the time)	7 (14)	9 (18)
Almost always or always	3 (6)	18 (36)
Answer to question 4 of the IIEF regarding the 'frequency of the erection maintenance'		
Not concerned	11 (22)	7 (14)
Almost never or never	17 (34)	6 (12)
A few times (much less than half the time)	6 (12)	6 (12)
Sometimes (about half the time)	6 (12)	4 (8)
Most times (much more than half the time)	8 (16)	10 (20)
Almost always or always	2 (4)	17 (34)
Evolution of scores		
Question 3	1.9 ± 1.6	3.2 ± 1.8[a]
Question 4	1.8 ± 1.5	3.1 ± 1.9[a]

[a] $P \leqslant 0.0001$. Worst possible evolution = –5, best possible evolution = +5.

Table 4. Evolution of scores for IIEF domains

IIEF domain	IIEF score				
	Before treatment	After treatment	Mean evolution	Best possible evolution	*P* value
Erectile function	11.4 ± 7.5	19.3 ± 9.9	+8.1 ± 9.2	+29	$P \leqslant 0.0001$
Orgasmic function	5.4 ± 3.9	6.9 ± 3.3	+1.45 ± 3.8	+10	$P = 0.0033$
Sexual desire	6.3 ± 2.3	6.9 ± 1.9	+0.6 ± 1.9	+8	$P = 0.0349$
Intercourse satisfaction	5.3 ± 3.9	9.4 ± 4.8	+4.2 ± 4.3	+15	$P \leqslant 0.0001$
Overall satisfaction	4.0 ± 2.2	6.7 ± 3.1	+2.6 ± 3.2	+8	$P \leqslant 0.0001$

was statistically different from the post-transplant score (3.1 ± 1.9, $P < 0.0001$). Overall, 58% of patients answered 'sometimes', 'a few times' or 'almost never or never' at visit V1. At the final visit, 54% of patients answered 'almost always or always' or 'most times.

For these two items of the IIEF no relationship was found between the evolution of the score obtained and the presence or not of a dialysis, the duration of the dialysis or the duration of the last transplant. When responses at baseline were examined by the cause of ED (psychogenic, organic or mixed), those with a mixed cause ($n = 36$) gave similar responses to the intent-to-treat population, while those with an organic cause ($n = 13$) had a much poorer erection ability. Only one individual had an exclusively psychogenic cause of ED.

Secondary efficacy parameters. The focus of the secondary efficacy parameters was to determine the effect of sildenafil treatment on patient quality of life and patient satisfaction with treatment. To achieve this a number of assessment instruments were used. The evolution of scores for the five domains of the IIEF: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction, are shown in Table 4. All domains showed a statistically significant improvement after treatment, although the evolution of the score for sexual desire was much smaller than those reported for the other domains.

The analysis of the answers to question 7 of the IIEF (over the past 4 weeks, when you attempted sexual intercourse, how often was it satisfactory for you?) showed that most patients (66%) answered 'sometimes', 'a few times' or ' almost never or never' at visit V1. At the final visit, 50% of the patients answered 'almost always or always' or 'most times.'

Responding to the Global Efficacy Assessment Question: at the end of the study, globally, did the treatment that you have taken improve your erections, 33 patients (66%) replied yes and 11 patients (22%) replied no. Data were not available for six of the 50 patients (12%) in the intent-to-treat population.

The EDITS questionnaire determined whether patients were satisfied with treatment on a scale from 0 (worst score possible) to 100 (best score possible). The mean score was 66.8 ± 24.4. Overall, 38% of patients had a score $\geqslant 75$ and 60% of patients had a score $\geqslant 50$. Data were missing for 20% of patients. The data demonstrate that patients were relatively satisfied with treatment.

The LISAT questionnaire evaluated satisfaction with different domains of life. Scores obtained at the end of treatment for the items: 'your life as a whole', 'your family life', 'your contact with friends and acquaintances', 'your leisure situation', 'your vocational situation' and 'your financial situation' between inclusion visit and the final visit were not statistically different. However, for sexual life and partnership relation the scores were significantly different: +1.9 ± 1.6 ($P \leqslant 0.0001$) and +1.1 ± 1.6 ($P \leqslant 0.0001$), respectively.

Safety

The safety analysis was performed on 51 patients as three patients had not taken the study treatment. Overall, 30 patients (58.8%) presented with at least one adverse event during the study. Most of them were mild to moderate. Adverse events that may have been related to study drug were reported by 17 patients (33.3%) and in general were consistent with the known side effects of sildenafil: hot flushes, headache and abnormal vision. The most frequently observed adverse events (incidence > 3% of patients treated) are shown in Table 5. Five patients (9.8%) presented with at least one serious adverse event, which led to three patients being withdrawn from the study. Only two of the serious adverse events were considered possibly attributable to the study drug. One patient developed an angina pectoris 1 day after the beginning of treatment and another presented with a non-serious aggravated depression.

Values for clinical laboratory measurements are shown in Table 6. Serum creatinine levels increased

Table 5. Most frequently reported adverse events

Adverse event	Number (%)
Headache	9 (17.6)
Abnormal vision	3 (5.9)
Abdominal pain	3 (5.9)
Vomiting	2 (3.9)
Hot flushes	2 (3.9)
Palpitation	2 (3.9)
Creatinaemia	2 (3.9)

Table 6. Evolution of laboratory parameters in patients who completed the study

Parameter	Before treatment	End of the study	Evolution with treatment
Serum creatinine level (μmol/l) ($n=43$)	131 ± 31	136 ± 37	$+4.88 \pm 14.48$[a]
Fasting hyperglycaemia (g/l) ($n=5$)	0.97 ± 0.11	1.15 ± 0.77	$+0.26 \pm 0.88$[b]
Post-prandial glycaemia (g/l) ($n=5$)	1.42 ± 0.34	2.14 ± 1.62	$+0.53 \pm 1.77$[c]
Glycolated haemoglobin (%) ($n=5$)	5.30 ± 0.73	7 ± 1.88	$+1.83 \pm 1.76$[d]
T_0 tacrolimus ($n=6$)	8.5 ± 1.13	8.2 ± 4.54	-1.63 ± 6.48[e]
T_0 cyclosporine ($n=33$)	136.5 ± 91.8	115 ± 37.6	-25.77 ± 90.74[f]

Wilcoxon test, P values. [a]$P=0.047$, [b]$P=0.87$, [c]$P=1$, [d]$P=0.25$, [e]$P=0.37$, [f]$P=0.3$.

slightly between baseline and the end of the study. The mean change was $+4.9 \pm 14.5$ ($P=0.0474$). There were no significant increases in levels of fasting blood sugar, post-prandial sugar and glycolated haemoglobin in patients with pancreatic transplants. There was no statistically significant evolution in the trough blood levels of the immunsuppressants tacrolimus and cyclosporine between inclusion and the end of the study.

Discussion

Studies have shown that many renal transplant recipients continue to suffer ED despite improvements to their general physiology following the transplant [9,16,17]. The goal of treatment in these individuals is therefore to provide adequate sexual function without creating significant risk of damage to the transplanted organ.

The results of the two IIEF questions that formed the primary efficacy parameter show that sildenafil treatment significantly improved patient's erection ability to attain and maintain an erection sufficient for intercourse.

Analysis of the secondary efficacy parameters confirmed these results. Indeed the evolution of the score from start to end of study was statistically significant for all five domains of the IIEF which addressed the functional aspects of the pathology (erectile function and orgasmic function), the psychological aspects (sexual desire) and patient satisfaction (intercourse satisfaction and overall satisfaction). Although statistically significant, the score for sexual desire was lower than those of the other domains measured. However, as sildenafil does not act on desire, this is most likely secondary to improvements in erectile function itself.

The Global Efficacy Questionnaire revealed that 66% of patients believed treatment had improved their erections, as compared with 73% on the non-transplant population of the same study (data not shown). This was confirmed by a successful intercourse rate after treatment of 61.8% at the end of the study. This is in accordance with the results of another study [18]. The response to the global efficacy questionnaire was analysed according to a number of different variables. The results showed that overall patient satisfaction did not appear to be influenced by the age of the patient, the cause or duration of ED or the presence or absence of nocturnal erections.

Patient satisfaction with sildenafil was also assessed by the EDITS questionnaire. A mean score of 66.8, on a scale from 0 to 100 demonstrated that patients were satisfied with treatment. This high index of satisfaction coupled with the frequency that patients took sildenafil (on average 3.5 capsules/week) shows how important a normal sexual life is to patients after transplantation. Further evidence that sildenafil can improve quality of life in these patients was provided by analysis of the LISAT questionnaire, which revealed that: a patient's sexual life and relationship with their partner, two important aspects of overall quality of life, were improved by sildenafil treatment.

Before selecting a drug therapy for a renal transplant population, a careful assessment must be made of potential interactions with the immunosuppressive therapy the patients are receiving and any possible effect on the graft function. Concurrent disease states, such as renal or hepatic impairment, or concomitant use of inhibitors of the cytochrome P450 isozyme CYP3A4 could increase systemic exposure to sildenafil.

A slight increase in serum creatinine levels between the inclusion visit and the end of the study ($+4.88 \pm 14.48$ μmol/l, $P=0.0474$) was observed. No renal biopsies were performed, suggesting that physicians were not concerned about this increase. In addition, there is no evidence for a causal relationship between this increase and sildenafil administration. Few data are available to date on the effects of sildenafil on renal function. Rostaing *et al.* [19] demonstrated an increase of the glomerular filtration rate in a small cohort of 10 patients receiving sildenafil citrate. It is worth noting that among the 28 patients having an abnormal value of creatininaemia at the end of the study, the value at inclusion was normal only for one patient and already abnormal for the 27 other patients (up to twice normal laboratory value. One can speculate on the reasons for the serum creatinine level increase observed in our study. For example, no difference was found in BP at the beginning (systolic BP $=140 \pm 13$ mmHg, diastolic BP $=81 \pm 8$ mmHg) or at the end of the study (systolic BP $=140 \pm 16$ mmHg, diastolic BP $=82 \pm 11$ mmHg), nor in weight gain (difference $=0.08 \pm 1.96$ kg, $P=0.76$). From a clinical point of view, an increase of 5 μmol/l of serum creatinine is of limited value.

Patients with severe renal impairment (creatinine clearance <30 ml/min) have a reduced clearance of sildenafil. Plasma levels in patients with severe renal impairment are therefore approximately twice those found in healthy subjects. There are no significant effects on the metabolism of sildenafil in subjects with moderate (creatinine clearance 30–49 ml/min) or mild (creatinine clearance 50–80 ml/min) renal impairment [20]. This probably explains why we found a similar percentage of patients taking 100 mg in both transplant (53%) and non-transplant (44%) cohorts of the study.

Slight modifications of the glycaemic control were also observed in the pancreas recipients. However, none reached the statistical significance level. Given the very small number of patients ($n=5$), no conclusion can be drawn from this part of the study. It is known from previous sildenafil trials [21,22] that this drug does not interact with the glycaemic homeostasis.

Cyclosporine and tacrolimus are metabolized primarily by the cytochrome P450 enzyme, CYP3A4, in the liver and small intestine. Drugs that either induce or inhibit CYP3A4 may therefore alter the pharmacokinetics of these immunosuppressive agents. Sildenafil is a very mild inhibitor of CYP3A4. However, in this study concomitant administration of sildenafil with tacrolimus and cyclosporine did not lead to a rise in the trough blood levels of these immunosuppressive drugs. This is in accordance with the findings of others [23]. Furthermore, as cyclosporine and tacrolimus are substrates and not inhibitors of CYP3A4, the major metabolic pathway for sildenafil, they should not inhibit sildenafil metabolism.

Conclusion

This study extends the benefits of sildenafil to a population of renal transplant patients with normal or subnormal graft function. However, it should be confirmed by a randomized, placebo controlled, double blinded study. Treatment with sildenafil significantly increased patient's erection ability and the frequency of their erection maintenance. Patients reported improvements in their relationships with partners and in their sexual quality of life, and a large proportion were satisfied with treatment. Sildenafil was well tolerated and had no interaction with immunosuppressive drugs or adverse effects on grafted tissue. Physicians therefore have at their disposal an effective and well-tolerated oral agent for the management of ED in renal transplant patients.

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