CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 20, NO. 9, 2004, 1377–1384

0300-7995
doi:10.1185/030079904X2394

BRIEF REPORT

Preliminary observations on the use of propionyl-L-carnitine in combination with sildenafil in patients with erectile dysfunction and diabetes

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Key words: **Diabetes mellitus, type 1 – Diabetes mellitus, type 2 – Erectile dysfunction – Propionyl-L-carnitine – Sildenafil**

SUMMARY

Purpose: To investigate the efficacy and tolerability of oral propionyl-L-carnitine (PLC) plus sildenafil in men with erectile dysfunction (ED) and diabetes unresponsive to sildenafil monotherapy.

Materials and methods: Patients with medically documented ED of organic or mixed aetiology and diabetes (type 1 and 2) were randomised to receive oral PLC (2 g/day) plus sildenafil (50 mg twice weekly) (20 patients, Group 1) or sildenafil alone (20 patients, Group 2), in a double-blind, fixed-dose study. All patients had been previously treated unsuccessfully with a minimum of eight administrations of sildenafil. Efficacy was evaluated using the International Index of Erectile Function (IIEF) questionnaire: total score, subscores for questions 3 (Q3; achieving an erection) and 4 (Q4; maintaining an erection) and global efficacy question (GEQ: 'Has treatment improved your erections?'). Patients Event Logs were also used.

Results: After 24 weeks of treatment, mean scores for IIEF Q3 and Q4 had improved significantly in patients of Group 1 (4.25 ± 0.63 and 3.95 ± 1.0) compared with Group 2 (2.9 ± 0.71 and 2.7 ± 0.96) ($p < 0.01$). Moreover, the percentage of patients with improved erections (GEQ 68% vs. 23%) and successful intercourse attempts (76% vs. 34%) was significantly increased in Group 1 compared with Group 2 ($p < 0.01$). Fourteen (70%) patients in Group 1 and four (20%) in Group 2 reported an increase in mean IIEF EF domain score of ≥ 4 ($p < 0.01$). Treatments were well tolerated and no patient discontinued study medication. Two patients in Group 1 reported mild gastric pain.

Conclusions: Salvage therapy with PLC plus sildenafil was more effective than sildenafil in the treatment of ED in patients with diabetes refractory to sildenafil monotherapy.

Introduction

The World Health Organization estimates that over 135 million people worldwide have diabetes with 300 million cases predicted by the year 2025[1]. Equally, ED has gone from a little discussed, poorly diagnosed condition to one that is now recognised as very common with an estimated global prevalence of 152 million men (322 million predicted by 2025)[2]. ED is a common complication of diabetes (three-fold increase in the

subset of patients with diabetes), which occurs at an earlier age than in non-diabetic men[3]. Researchers have suggested that ED coexists with other diseases because they share common risk factors and recent epidemiological studies support this proposition. A cohort study conducted in the United States using a managed care claims database showed a 20.2% prevalence of diabetes mellitus in male health care plan members with ED[4], while the multinational MALES (Men's Attitudes to Life Events and Sexuality) study showed an overall prevalence of ED of 16% with 39% of men with diabetes reporting ED[5].

ED in patients with diabetes can be caused by a number of interrelated mechanisms, including vascular disease, endothelial dysfunction, autonomic neuropathy, hormone imbalance and the use of multiple medications. Patients with diabetes have been shown to have impaired endothelium-mediated relaxation of blood vessels and diabetes-associated macrovascular lesions affecting the penile arteries and helicine arterioles may diminish blood supply to the corpus cavernosum. Endothelium-1, a powerful smooth muscle constrictor produced by endothelial cells in the corpus cavernous thought to enhance/modulate the effects of noradrenaline and nitric oxide, has been shown to affect erectile function in patients with diabetes[6].

Since its introduction, sildenafil citrate, with its demonstrated effectiveness and tolerability in a broad range of patients, has transformed ED treatment[7]. Combined data from 11 double-blind, placebo controlled trials, show improved erections in 83% of non-diabetic subjects receiving sildenafil, while 59% of patients with type 1 and 63% with type 2 diabetes reported improvements[7]. Despite the good efficacy of sildenafil in treating ED in patients with concomitant diabetes, response rates are consistently lower than in other disease-specific populations. The fact that no single treatment is suitable or effective for diabetic men with ED prompted investigators to study new pharmacological strategies using combinations of diverse agents acting at different levels within the erectile process.

Propionyl-L-carnitine (PLC) a short-chain fatty ester of carnitine (3-hydroxy-4-*N*-trimethyl-aminobutyric acid) is a naturally occurring substance required in mammalian energy metabolism[8,9]. Carnitine has shown beneficial effects in vascular conditions including peripheral arterial disease and diabetic neuropathy, and there is evidence that it is effective combined with verapamil in advanced and resistant Peyronie's disease[10–12]. Although the mechanism of action of PLC remains incompletely understood, it appears that its cardiovascular effects are in part related to vasodilatation and enhanced blood flow[13]. Cavallini *et al*. reported that PLC protects and restores cells with damage caused by inflammation and ischaemia, down-regulates most mediators of inflammation and up-regulates aerobic metabolism[12]. In an experimental model of diabetes, PLC improved motor performance apparently due to a protective effect on the microcirculation, since PLC has no known hypoglycaemic effect[14].

The observation that PLC can exert a beneficial effect in a range of different pathologies involving both vascular and muscle tissues, together with the increasing prevalence of ED and diabetes and the lack of an effective management strategy for these patients, stimulated the search for PLC activity in this important subpopulation. In a randomised, double-blind trial we compared the activity of PLC plus sildenafil with that of sildenafil alone in patients with ED and diabetes.

Materials and methods

This randomised, double-blind, fixed-dose study was performed in Italy from June to December 2002. The trial consisted of a 4-week run-in phase, during which baseline data on sexual function were collected, followed by a 24-week double-blind phase in which patients received either combination therapy or monotherapy. All patients gave their written informed consent.

To be eligible patients had to be 18 years of age or older with medically documented ED and be in a stable relationship of more than 6 months with a female partner. Diagnosis of ED was based on the patient's medical history, physical examination, standard laboratory tests and responses to the International Index of Erectile Function (IIEF) questionnaire. Patients had to have a clinical diagnosis of type 1 diabetes of at least 5 years duration or a clinical diagnosis of type 2 diabetes of at least 2 years duration, as defined by the National Diabetes Data Group[15]. Medical management of diabetes had to be generally stable for 6 months before study entry, with HbA_{1C} levels < 11% and FPG < 300 mg/dL. Biochemical parameters were monitored throughout the study.

Patients were excluded if they presented with: genital anatomical deformities; a primary diagnosis of a sexual disorder other than ED, a poorly controlled major psychiatric disorder, a recent history of major haematological, renal or hepatic abnormalities, myocardial infarction, stroke, heart failure, unstable angina or hypotension, or treatment with nitrates. Also excluded were patients who had one of the following: $HbA_{1C} \geq 11\%$, recurrent hypoglycaemic episodes, severe disabling neuropathy, Cushing's syndrome, diabetes secondary to pancreatic damage or acromegaly.

Treatment Plan

After a 4-week run-in period, during which baseline data and sexual function were collected, patients were randomised to receive either PLC 2 g/day (Dromos*) plus sildenafil 50 mg (Viagra†) twice weekly (Group 1) or sildenafil 50 mg alone twice weekly (Group 2) for 24 weeks. Patients in Group 2 were instructed to take sildenafil in addition to placebo tablets identical in packaging and appearance to PLC tablets. Each patient was randomly assigned a code number and the study drugs were provided to patients in bottles labelled with their corresponding codes. The randomisation code was not known to investigators or patients but known to the nurses. The coding was revealed only at the end of the study.

Efficacy Assessments

The primary outcome measures were:

1. International Index of Erectile function (IIEF)[16], week 0 and week 24. Question 3 (assesses the ability to achieve an erection sufficient for sexual intercourse). Question 4 (assesses the ability to maintain an erection after penetration).
2. Answers were scored from 1 (almost never/never) to 5 (almost always/always), with 0 indicating no sexual activity.

The secondary outcome measures were:

1. Event Log of erectile function: pre-treatment 4-week run-in period through to week 24 of treatment, completed by patients each time they engaged in sexual activity. This asked about response to study drug and success of intercourse attempts.
2. Global Efficacy Question (GEQ), week 24:
   This question asked, 'Has the treatment you have been taking over the past 4 weeks improved your erections?'

3. IIEF EF domain[16], week 0 and week 24.

The IIEF questionnaire consists of 15 questions grouped into five different domains:

- Erectile function:
  Questions 1–5 and 15 (score range, 1–30).
- Intercourse satisfaction:
  Questions 6–8 (score range, 0–15).
- Orgasmic function:
  Questions 9–10 (score range, 0–10).
- Sexual desire:
  Questions 11–12 (score range, 2–10).
- Overall satisfaction:
  Questions 13–14 (score range, 2–10).

Vascular evaluations were carried out using pharmacopenile duplex ultrasonography (PPDU). The integrity of penile blood flow and veno-occlusive function were determined by measuring right and left cavernosal artery peak systolic velocity (PSV), end diastolic velocity (EDV) and resistance index (RI) before and after pharmacological stimulation with PGE1 (10 μg) intracavernosally. PSV and EDV were measured at baseline and at the end of the study. RI was calculated from PSV and EDV (PSV–EDV/PSV).

Tolerability was assessed throughout the study and all adverse events occurring during or within 7 days of the end of treatment were recorded. Dropout rate also served as a measure of tolerability. A serious adverse event (SAE) was defined as one that was fatal, life threatening, resulted in permanent disabilities, required hospitalisation, or was a congenital anomaly, cancer or drug overdose.

Statistical Analyses

Quantitative data (mean scores for IIEF Q3, Q4 and EF domain, PSV, EDV, RI) were assessed between groups and before vs. after treatment using Student's T tests: paired T tests in the same group of patients (before vs. after) and unpaired T tests between the two treatment groups (Group 1 vs. Group 2). Due to the small sample size, Fisher's tests (not chi-squared tests) were used to analyse qualitative data (side-effects, responses to the GEQ and the percentage of successful attempts at intercourse) to compare groups before and after therapy. All analyses of significance were 2-sided and tested at the 5% level.

Results

Forty patients (mean age 64 years) with diabetes and a clinical diagnosis of ED were enrolled in the study. All patients had previously been treated unsuccessfully with a minimum of eight administrations of sildenafil and PPDU confirmed the presence of moderate/severe vasculopathy. Twenty patients were randomised to receive PLC plus sildenafil (Group 1) and 20 to receive sildenafil alone (Group 2). Baseline characteristics including age, duration of disease, aetiology and duration

* Dromos is a trade name of Sigma–Tau, Rome, Italy
† Viagra is a trade name of Pfizer Inc.

Table 1. Demographics, concomitant diseases and lifestyle factors at baseline in patients treated with propionyl-L-carnitine plus sildenafil (Group 1) or sildenafil alone (Group 2)

	Group 1	Group 2
Number of patients	20	20
Mean age (years; range)	63.7 (52–70)	64.1 (45–81)
Caucasian (%)	100	100
Erectile dysfunction aetiology (%)		
organic	64.6	65.7
mixed	35.4	34.3
Smoking status (%)		
ex-smoker	41.5	43.6
never smoked	26.7	27.2
smoker	31.8	29.2
Mean time since diagnosis of erectile dysfunction (years; range)	5.7 (0.7–22)	5.3 (0.6–19.5)
Diabetes type (%)		
Type 1	18	16
Type 2	82	84
Mean time since diagnosis of diabetes (years; range)	18.7 (1.7–36)	13 (1.3–38)
Diabetes treatment (%)		
insulin	18	16
oral antidiabetics	82	84
Concomitant diseases		
hypertension	31.4	33.6
peripheral vascular disease	4.3	3.4
other	3.1	2.3
HBA_{IC} (%)	8.6 (5.7–11.3)	8.4 (5.6–10.9)

of ED, duration of diabetes and metabolic control, were similar in both groups (Table 1). The aetiology of ED was organic in 64.6% of patients in Group 1 and 65.7% in Group 2; and mixed in 35.4% and 34.3% respectively. Mean time since diagnosis of ED was 5.7 (0.7–22 years) and 5.3 (0.6–19.5 years) in group 1 and 2, respectively. Baseline mean scores for EF domain were not significantly different in patients in the two groups (11.9 ± 2.6 in Group 1 vs. 10.4 ± 1.9 in Group 2). Management of diabetes remained unaltered throughout the study.

All forty patients were available for follow-up. After 24 weeks of treatment, there were marked improvements in the ability to achieve and maintain erections, with the mean scores for IIEF Q3 and Q4 significantly higher in Group 1 (4.25 ± 0.63 and 3.95 ± 1.0) compared with Group 2 (2.9 ± 0.71 and 2.7 ± 0.96) ($p < 0.01$) (Figure 1).

The percentage of successful intercourse attempts, as estimated by Patients Event Logs, increased from 11% to 34% in Group 1 and from 10% to 76% in Group 2 ($p < 0.01$). Positive responses to the GEQ ('Has treatment improved your erections?') were significantly higher in Group 1 with 68% of patients answering 'Yes' compared with 23% in Group 2 ($p < 0.01$).

Fourteen (70%) patients in Group 1 and 4 (20%) in Group 2 reported an increase in IIEF EF domain mean score of ≥ 4 ($p < 0.01$). Mean EF domain score increased from 11.9 ± 2.6 to 14.7 ± 2.9 in Group 1 (combination treatment) and from 10.4 ± 1.9 to 11.2 ± 2.0 in Group 2 (monotherapy) (Figure 1). Treatment with sildenafil alone did not cause significant changes in IIEF EF scores, while significant differences were found both before and after combination therapy and between PLC plus sildenafil and sildenafil alone (both $p < 0.01$). Haemodynamic parameters (PSV, EDV and RI) were not significantly different following treatment in either group (Table 2).

No patient discontinued study medication. Both treatments were well tolerated with two patients in Group 1 reporting mild gastric pain. No SAEs were observed.

Discussion

Men with ED and diabetes constitute a particularly difficult-to-treat subpopulation. Sildenafil is the initial treatment of choice not only for men with ED but also

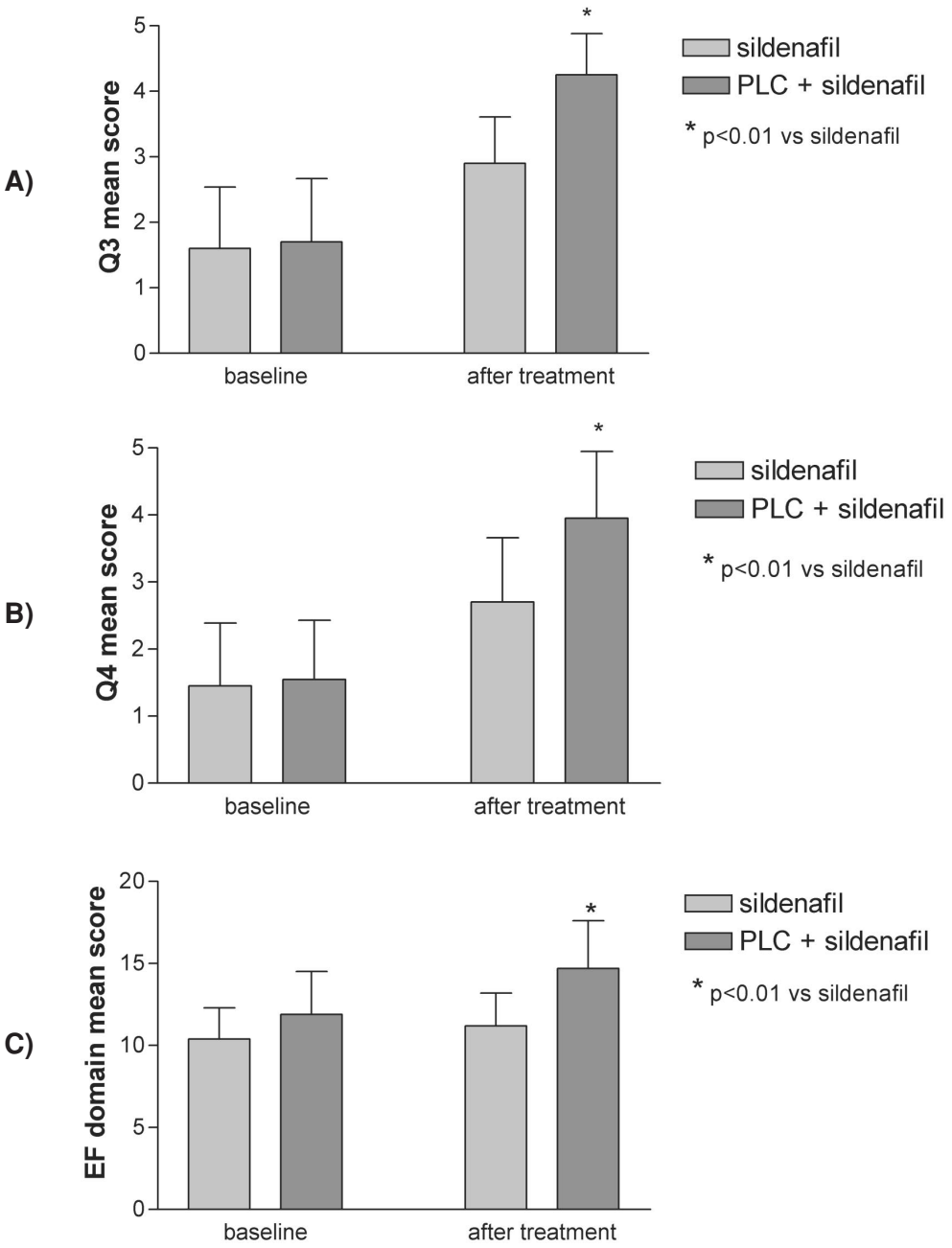

Figure 1. *International Index of Erectile Function (IIEF) scores (mean ± SD) before and after combination therapy with propionyl-L-carnitine plus sildenafil (Group 1) and sildenafil alone (Group 2) (n = 40): A) Question 3 (Q3); B) Question 4 (Q4); C) IIEF EF domain*

Table 2. *Right and left cavernosal artery peak systolic velocity (PSV), end diastolic velocity (EDV) and resistance index (RI) before and after treatment with propionyl-L-carnitine plus sildenafil (Group 1) and sildenafil alone (Group 2) (n = 40)*

Haemodynamic parameter (mean ± SD)	Before treatment		After treatment		*p*
	Group 1	Group 2	Group 1	Group 2	
Right cavernosal artery PSV (cm/sec)	27.7 (4.3)	26.2 (4.0)	28.7 (3.8)	27.0 (3.3)	NS
EDV (cm/sec)	6.0 (1.3)	5.9 (1.3)	6.0 (1.5)	6.0 (1.3)	NS
RI (%)	76.5 (7.8)	76.0 (7.2)	77.5 (7.8)	76.7 (6.7)	NS
Left cavernosal artery PSV (cm/sec)	27.7 (4.0)	26.4 (4.5)	28.7 (3.6)	27.3 (3.6)	NS
EDV (cm/sec)	6.0 (1.3)	6.5 (1.3)	5.9 (1.4)	6.2 (1.5)	NS
RI (%)	76.9 (6.7)	75.3 (8.1)	77.2 (6.7)	76.2 (7.8)	NS

NS = Not significant

for those with concomitant diabetes. High response rates (> 80%) have been reported in non-diabetic men but in the subgroup with diabetes responses are significantly lower (59% and 63% of men with type 1 and type 2 diabetes, respectively)[6,7]. These patients may respond to second-line oral therapy or combination treatment[6,7]. In their review, Koppiker *et al*. concluded that the use of combination therapy for ED has not been adequately evaluated[6]. To our knowledge, this is one of the few studies investigating the use of oral combination therapy in patients with ED and diabetes.

The principal results indicate that PLC plus sildenafil for 6 months was an effective oral therapy for men with diabetes as determined by the IIEF (question 3 and 4 and EF domain), the GEQ and the percentage of successful attempts at intercourse.

On enrolment, patients were considered to be non-responders to first-line sildenafil (taken for at least eight consecutive occasions) with low mean scores for IIEF Q3 and IIEF Q4 and a low percentage of successful attempts at baseline. All this appears to be confirmed by an increase of mean score for IIEF EF domain, following monotherapy with sildenafil, in only four patients (20%). What is not clear, however, is the reason for the very low response in these patients. In most trials in men with ED and diabetes, sildenafil is started at 25 mg or 50 mg and titrated to 100 mg depending on efficacy and tolerability. Dey *et al*. concluded that sildenafil should be titrated up to 100 mg for an effective response while Price *et al*. reported significant responses with a single 50 mg dose[17,18]. It cannot be excluded that the sildenafil doses used in our trial were insufficient to elicit a clinical response. However, patients in this study were older than those in similar trials and it is known that the clearance of sildenafil is reduced in elderly patients, with plasma concentrations increased by about 40% in patients over 65 years[19]. Concerns about age-related tolerability (headache, flushing, dyspepsia, visual disturbances) discouraged us from attempting a dosage increase in our patients. It seems, however, that, irrespective of the dosage used, there is a subpopulation of diabetic patients that is unresponsive to sildenafil. The question remains why do these patients not respond? It was initially proposed that age and duration of ED/diabetes may be predictive of a response but Korenman *et al*. found no significant differences in treatment results across the subcategories of age and duration of ED/diabetes[20].

ED in patients with diabetes can be caused by many interrelated mechanisms. Insulin causes release of NO from the endothelium and subsequent vasodilatation and increased blood flow in insulin-sensitive individuals[6]. In insulin-resistant patients including those with diabetes, endothelial response to insulin is reduced with a subsequent decrease in the production of NO and cGMP in the corpus cavernosum. This reduction in the bioavailability of NO, fundamental in the erectile process, may contribute to diabetes-associated ED. Poor vascular supply to the penile arteries caused by macro-vascular disease and atherosclerotic lesions also diminishes blood supply to the corpus cavernosum and limits the response to increased demand during sexual stimulation. Impaired neurogenic and endothelium-mediated relaxation of penile arteries with a shift towards the vasoconstrictor pathways that favour detumescence may also play a role. Concomitant medications frequently used in diabetic patients including β-adrenergic blocking agents, sulfonylureas, calcium-channel antagonists and lipid-lowering agents can reduce the efficacy of sildenafil and in certain cases also contribute to ED[6].

In our study, 68% of patients of Group 1 reported improved erection (compared with 23% of Group 2), the number of successful attempts at intercourse in Group 1 (76%) was significantly higher compared with Group 2 (34%) and the mean IIEF EF domain score increased by ≥ 4 points in 70% of patients receiving PLC plus sildenafil compared with 20% of those receiving monotherapy.

This is the first study using this combination and as it was not designed to elucidate the putative mechanisms of action of such treatment in patients with ED and diabetes, definite conclusions cannot be drawn. However, reasonable hypotheses can be made based on data obtained with PLC in other studies. PLC has proven efficacy in enhancing vascular function. Cippola *et al*. found that PLC has a vasodilatory effect on small, human subcutaneous arteries precontracted with noradrenaline[13]. This effect was mostly mediated by endothelial production of prostaglandins but PLC also had a small effect on the vascular smooth muscle. They concluded that the beneficial cardiovascular effects of PLC may be (at least in part) related to vasodilatation and enhanced blood flow. Interestingly, they found that the production of NO was not likely to be involved in mediating the vasodilatory effects of PLC. In contrast, Herrera *et al*. showed that L-carnitine induced endothelium-dependent relaxation was mostly mediated by endothelial production of NO, suggesting a moiety-specific effect[21]. These results confirm earlier *in vitro* studies showing that in endothelial cells PLC was able to counteract metabolic changes induced by hypoxia and subsequent reoxygenation[22]. More specifically, oral PLC in combination with intraplaque verapamil significantly increased IIEF and reduced plaque size and penile curvature, disease progression and the need for surgery in patients with advanced and resistant Peyronie's disease[12]. PPDU of the cavernosal arteries with increased IIEF scores showed that treatment reduced EDV and increased the RI while PSV

remained unchanged suggesting erectile failure associated with Peyronie's disease is caused by venous leakage. The authors concluded that biochemically PLC and verapamil provide a more complete anti-inflammatory combination than standard therapy (tamoxifen and verapamil). A similar situation could have occurred in our study whereby the combination of PLC and sildenafil provided a more complete vasodilatory and enhanced blood flow effect than each agent given alone. Haemodynamic parameters remained unchanged in both treatment groups, an observation which requires additional investigation.

PLC and sildenafil were well tolerated and no clinically significantly changes in laboratory test results were observed, suggesting that PLC and sildenafil did not impair metabolic control. Importantly no patient discontinued combination therapy while discontinuation rates of up to 17% have been reported previously in diabetic patients treated with sildenafil monotherapy[23]. This seems to justify our decision not to increase the dose of sildenafil to 100 mg.

To date, few studies have been published on the use of combined oral therapy. One study investigating the effects of combined oral therapy with doxazosin and sildenafil in the treatment of non-organic ED refractory to sildenafil monotherapy, showed that the combination was well tolerated with significant increases in IIEF compared with sildenafil plus placebo[24], while studies using oral sildenafil and intraurethral alprostadil as salvage therapy in patients unresponsive to sildenafil alone show some synergistic effects[25]. These reports, combined with the results of our study would appear to add weight to the concept of using agents with varying pharmacodynamic properties acting at different levels in the erectile cascade in the treatment of patients refractory to single drug therapy. Of course, we are just at the beginning of our search for more effective agents in the treatment of ED and more work needs to be done before recommendations can be made.

Conclusions

The results of this initial study are promising and suggest that combined oral therapy with PLC and sildenafil may provide a new approach for treating diabetic patients with ED.

Acknowledgments

Sigma–Tau, Italy, supported the study and the publication of this manuscript.

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Paper CMRO-2690, *Accepted for publication*: 05 July 2004
Published Online: 16 July 2004
doi:10.1185/030079904X2394