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To ascertain whether oral propionyl-L-carnitine combined with intraplaque verapamil is a useful therapy for advanced or resistant Peyronie's disease.

The combined drugs were assessed in two studies. In the first, 60 patients with advanced Peyronie's disease, diagnosed using accepted definitions, were randomized in two subgroups treated with verapamil intraplaque infiltration (10 mg weekly for 10 weeks) plus a 3-month administration of propionyl-L-carnitine (2 g/day), or verapamil infiltration plus oral tamoxifen (40 mg/day) for 3 months. In the second study, 15 patients with resistant Peyronie's disease (progression despite previous therapy) received verapamil plus propionyl-L-carnitine. The differences between subgroups or between the variables before and after therapy were compared using analysis of variance or the chi-squared test.

In the first study, the reduction in pain was the same in both subgroups. Propionyl-L-carnitine plus verapamil significantly reduced penile curvature, plaque size, cavernosal artery end-diastolic velocity, the need for surgery and disease progression, and increased the International Index of Erectile Function score and resistivity index of the cavernosal arteries. Tamoxifen plus verapamil had none of these effects. No drug combination affected the peak systolic velocity. Patients receiving verapamil had no side-effects but those taking tamoxifen did. In the second study propionyl-L-carnitine and verapamil modified the disease patterns as in the first and no patient had side-effects.

The combination of propionyl-L-carnitine and verapamil can be considered the therapy of choice for advanced and resistant Peyronie's disease.

propionyl-L-carnitine, verapamil, tamoxifen, Peyronie's disease

We recently showed that oral acetyl-L-carnitine was significantly more active than tamoxifen in the treatment of early Peyronie's disease [1]; patient recruitment for this trial was concluded in December 1998. Soon afterward a new acyl ester of carnitine, propionyl-L-carnitine (PLC), became commercially available, which is more active than acetyl-L-carnitine and L-carnitine in preventing cutaneous inflammation of the rat [2] and in protecting small arteries from chemical vasculitis [3]. These properties were considered particularly interesting as the initial histological pattern of Peyronie's disease resembles acute vasculitis, i.e. perivascular infiltration of polymorphonuclear cells, lymphocytes, macrophages, plasma cells, mast cells, perivascular exudate, and the successive histological pattern mimics an exaggerated process of scar production, i.e. intensive macrophage and fibroblast activation, and subsequent fibrosis and calcification [4].

L-carnitine and its acyl esters (mainly PLC and acetyl-L-carnitine) are present in the vast majority of mammalian cells in a homeostatic equilibrium controlled by the enzymatic family of carnitine-acyl-transferase(s) and by an active and (acyl)-selective kidney tubular reabsorption system [5]. Thus exogenous carnitine and its esters cause minor side-effects (mild euphoria) only occasionally [6].

These data stimulated the search for PLC activity on Peyronie's disease. Most patients with Peyronie's disease (60–70%) present with advanced stages of disease, where the treatment of choice is an injection with verapamil into the plaque [4]; furthermore, 10–20% of Peyronie's disease progresses even after therapy, i.e. intraplaque injection with verapamil, with or without oral tamoxifen, extracorporeal shock waves, or ionophoresis [4]. Thus we compared the activity of oral PLC or tamoxifen (both with verapamil injection) in patients with advanced Peyronie's disease

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in a double-blind controlled study, and with a second group in a prospective study, assessed oral PLC and verapamil in patients who were resistant to other therapies.

The trial was approved by the ethics committee of our institution. In all, 123 patients were examined for Peyronie's disease (mean age 58 years, range 34–65) between 1 March 1999 and 31 August 2000. The disease was diagnosed from the case history, an objective examination, glycaemia, glycosuria and glycosylated haemoglobin levels, a pharmacologically induced erection using intracavernosal PGE1 (20 μg) or trimix (papaverine 20 mg + phentolamine 1 mg + PGE1 30 μg) when PGE1 failed [4], a photograph taken during erection in the outpatient clinic [4], basal and dynamic (with intracavernosal PGE1 10 μg) colour Doppler ultrasonography, sexological semi-structured interview, and an assessment using the International Index of Erectile Function (IIEF) [7]. The disease was staged in each patient from symptoms, an objective examination and Doppler ultrasonography (basal and dynamic, as already described [1,4]). Thirty-four patients (28%) were deemed to have early disease, and thus were excluded and given acetyl-L-carnitine treatment [1], while 89 (72%) were suitable for the present study; 14 declined to participate, 15 withdrew during the study and 60 completed it. All these men had advanced Peyronie's stages [1,4], with symptoms of pain during erection, penile curvature affecting vaginal penetration and/or erectile failure. The objective examination showed: no painful palpable scar(s); basal and dynamic Doppler patterns of hyperechoic lesions >2 cm^2 and/or septum or cavernosal tissue infiltration, and/or calcifications; and venous leakage. The mean (range) age of the patients was 59 (42–64) years and the mean (range) duration of symptoms before diagnosis 13 (7–18) months. Associated diseases were Dupuytren's disease in three (5%), diabetes in 12 (20%) and hypertension in 13 (22%). The 60 patients were randomly assigned to two equal subgroups, using random numbers [8]. The patients received 10 intraplaque infiltrations (one/week) with verapamil 10 mg [9] and PLC 1 g twice daily (group 1) or tamoxifen 20 mg twice/day (group 2) [10] for 3 months. These drugs were delivered in unmarked colour-coded boxes, whose code and content were unknown by the authors and patients, but known to the nurses; the coding was revealed only at the end of the study. Data were collected for 6 months after therapy when the initial assessments were repeated.

In a prospective study, oral PLC combined with intraplaque verapamil was administered to further patients with Peyronie's disease that was resistant to other therapies. Fifteen patients (mean age 56 years, range 39–63) were examined between 1 March 1999 and 31 August 2000 for Peyronie's disease which was progressing despite other therapies (Table 1). The disease was diagnosed and staged as before; all patients had advanced stages, as described. Their case history, objective examination and ultrasonography indicated progression of disease. Associated diseases were Dupuytren's disease in one, diabetes in six and hypertension in six. The mean (range) time from the last treatment was 4 (2–8) months. The patients received 10 intraplaque infiltrations (1/week) with verapamil 10 mg [9] and PLC 1 g twice daily for 3 months. All patients gave fully informed consent for the treatment. Data were collected for 6 months after therapy when the initial assessments were repeated.

The following variables were compared between the groups or before and after therapy. Pain during erection was assessed with an international pain scale [11] (0, no pain; 1, slight pain; 2, moderate pain; 3, severe pain), with results classified as positive or negative depending on whether the pain regressed. Penile curvature was measured as an angle, as described previously [4], using photographs taken in the outpatient clinic after a pharmacologically induced full erection. Plaque size was measured during a full

The treatments administered to 15 patients who had progressive disease despite therapy. These patients were treated with oral PLC and intraplaque verapamil

	*Treatments**				
Patients	*IV*	*IV+T*	*IV+E*	*Ionophoresis*	*ECSW*
1	+			+	+
2	+			+	+
3			+	+	+
4	+		+	+	+
5		+		+	+
6		+		+	+
7	+			+	+
8	+			+	+
9		+		+	+
10			+	+	+
11	+			+	+
12	+		+	+	+
13		+		+	+
14		+	+	+	+
15		+		+	+

*IV, intraplaque verapamil; T, tamoxifen 20 × 2 mg/day for 3 months; E, vitamin E 200–400 mg/day for 3 months; ECSW, extracorporeal shock waves, 3000–4000 per session for six sessions. Ionophoresis, 12 sessions (three/week) using verapamil + dexamethasone at the positive pole for 20 min.

BJU International 77121-40 7/3/02 18:24:48 Rev 7.51a/W (May 2 2001)
The Charlesworth Group, Huddersfield 01484 517077

erection using ultrasonography, and the IIEF-15 score obtained. Peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistivity index (RI) of the left and right cavernosal arteries were measured using dynamic colour Doppler ultrasonography (with intracavernosal PGE1) [4]. The dorsal artery PSV, EDV and RI data were also assessed but not presented for brevity. The progression of disease was defined as an increase in plaque size, and/or penile curvature, and/or pain during erection, and/or EDV; and/or a decrease in RI, PSV and/or the IIEF score [4], with the results classified as progression or no progression. The need for surgery was recorded, i.e. a Nesbitt or Nesbitt plus prosthesis, with results classified as need for surgery or not. Side-effects were classified as their presence or absence.

Differences in pain, progression, need for surgery and side-effects were analysed using the chi-squared test to compare groups before and 6 months after therapy. Differences in plaque size, penile curvature, IIEF score, PSV, EDV and RI were assessed between the groups and before vs 6 months after therapy using ANOVA in a 2×2 factorial plan in the double-blind controlled trial, while a randomized block (1 patient = 1 block) ANOVA was used to assess the differences before vs 6 months after therapy in the prospective study. RI data were adjusted by angular transformation [$\sin^{-1} \sqrt{(p/100)}$] [8].

In the double-blind controlled trial, 29 patients (97%) in both groups reported a reduced pain score, while one did not. The effects of therapy on penile curvature are shown in Table 2. PLC with verapamil significantly reduced penile curvature and plaque size, while tamoxifen with verapamil did not. The effects of therapy on the IIEF-15 scores are also shown in Table 2, where for brevity only the score for sexual function is presented. PLC with verapamil significantly increased the IIEF score while tamoxifen with verapamil did not. The effects of therapy on right and left cavernosal artery PSV, EDV and RI are also shown in Table 2. PLC significantly reduced EDV and significantly increased RI, while tamoxifen with verapamil did not. The PSV was unchanged in both subgroups; the effects were the same for left cavernosal artery values. No patient in group 1 had disease progression, while six in group 2 did (chi square 4.629; $P < 0.05$). One patient in group 1 needed surgery (a Nesbitt operation was proposed but he refused) while 29 (98%) did not; in group 2, eight (27%) required surgery while 22 (73%) did not (chi square 4.615, $P < 0.05$). A Nesbitt with semi-rigid prosthesis (five) or Nesbitt alone (three) were proposed to these last patients; five accepted and three refused surgery. No patient in group 1 had side-effects, while six (20%) did so in group 2 (chi square 4.629; $P < 0.05$). The side-effects were mild epigastralgia (three) and mild loss of libido (three), but no patient discontinued therapy because of side-effects.

In the prospective study, nine patients had pain before therapy and six did not, while one still had pain after therapy and 14 did not (chi square 7.35; $P < 0.01$). The effects of therapy on penile curvature are shown in Table 3. PLC with verapamil significantly reduced penile curvature and plaque size. The effects of therapy on the IIEF-15 score are also shown in Table 3, and again only the score for sexual function is presented; the treatment significantly increased the IIEF score. PLC with verapamil significantly reduced the EDV and increased RI, while PSV was unchanged; the effect

Comparisons between penile curvature, plaque size and cavernosal artery values before and after therapy for the two subgroups, A and B, of 30 patients each, where A received PLC and verapamil, and B verapamil and tamoxifen

	Before therapy		*After therapy*		P		
Mean (SD) variable	*A*	*B*	*A*	*B*	*A vs B*	*Before vs after*	*Interaction*
Penile curvature,°	39.4 (4.2)	38.5 (36.6)	27.6 (6.7)	36.6 (5.6)	<0.01	<0.01	<0.01
Plaque size, mm²	31.8 (4.6)	33.2 (4.6)	24.2 (5.51)	31.9 (7.6)	<0.01	<0.01	<0.01
IIEF score	19.0 (5.7)	18.2 (5.9)	27.0 (3.3)	18.6 (7.8)	<0.01	<0.01	<0.01
Right cavernosal artery							
PSV, cm/s	34.7 (4.5)	35.3 (4.6)	34.8 (5.2)	35.3 (5.0)	NS	NS	NS
EDV, cm/s	15.6 (5.2)	14.5 (4.8)	7.3 (3.9)	12.9 (6.2)	<0.05	<0.01	<0.01
RI, %	47.5 (10.6)	49.8 (10.2)	62.7 (9.6)	51.7 (15.0)	<0.01	<0.05	<0.01
Left cavernosal artery							
PSV, cm/s	34.7 (4.3)	34.9 (4.3)	34.6 (4.6)	34.6 (4.7)	NS	NS	NS
EDV, cm/s	15.5 (4.9)	14.1 (5.0)	7.5 (4.2)	13.6 (6.0)	<0.05	<0.01	<0.01
RI, %	47.6 (10.1)	50.5 (10.8)	62.6 (10.0)	50.0 (15.0)	<0.05	<0.01	<0.01

BJU International 77121-40 7/3/02 18:24:49 Rev 7.51a/W (May 2 2001)
The Charlesworth Group, Huddersfield 01484 517077

Comparison between penile curvature, plaque size and cavernosal artery values before and after therapy in 15 patients with resistant Peyronie's disease

Mean (SD) variable	*Before therapy*	*After therapy*	P *(patients)*	P *(treatment)*
Penile curvature,°	42.0 (5.1)	37.5 (6.0)	<0.01	<0.01
Plaque size, mm^2	38.5 (4.9)	32.7 (6.4)	<0.01	<0.01
IIEF score	20.5 (3.6)	26.5 (4.0)	NS	<0.01
Right cavernosal artery				
PSV, cm/s	40.5 (6.0)	40.5 (5.4)	<0.01	NS
EDV, cm/s	14.8 (5.9)	7.3 (5.1)	<0.01	NS
RI, %	53.2 (8.3)	65.2 (10.1)	NS	<0.01
Left cavernosal artery				
PSV, cm/s	40.1 (6.5)	40.0 (6.6)	<0.01	NS
EDV, cm/s	14.1 (4.5)	8.3 (4.7)	NS	<0.01
RI, %	53.3 (8.1)	63.0 (9.8)	NS	<0.01

was the same on the left cavernosal artery (Table 3). Three patients required a Nesbitt procedure (two accepted and one refused); in one patient the disease progressed despite PLC and verapamil. No patient had side-effects.

Acetyl-L-carnitine is more active than tamoxifen in the therapy of Peyronie's disease [1] but when patient recruitment ended for that trial, PLC became available. A pilot study on a few patients showed that oral PLC with verapamil was significantly more active than acetyl-L-carnitine and verapamil in reducing scarring and penile curvature (G. Cavallini and G. Biagiotti, unpublished data). It was considered unlikely that the greater activity of PLC than acetyl-L-carnitine was caused by higher local bioavailability, as there is no difference in plasma transport among carnitine and its esters [12]; thus there must be real biochemical differences involved [5] and the present trial was started.

The advanced stage of the disease was assessed, as it remains an intriguing clinical problem for which several approaches have been used [4], mainly because 10–20% of patients progress despite therapy. Disease progression of Peyronie's precludes surgical correction of the penile deformity [4], and thus such patients are incurable. Hence 15 patients whose disease was refractory to several therapies were included in the study in a simple prospective design, because of the large variety of previous approaches.

We selected oral drugs (PLC and tamoxifen) to accompany verapamil injections, as these proved to be the most active approach to fibro-calcific scar(s) [4]. Oral tamoxifen was used as the positive control in the first study as, despite a recent but statistically questionable report [13], it was active in a large population of patients with early and advanced Peyronie's stages, while other drugs (vitamin E, tocoferols, allopurinol) were similar to placebo [4]. Previously we reported that acetyl-L-carnitine is more active than tamoxifen in the early stages only [1], and thus it was considered unsuitable for advanced Peyronie's disease. The use of a positive control (tamoxifen) was preferred to placebo, as we were seeking a drug more active than those currently available.

The tamoxifen and verapamil dosage were selected from previous papers [4,9,10,13], and PLC from a preliminary assessment using 1, 2 and 3 g/day, in which 2 g/day was as effective as 3 g/day but was expected to induce fewer side-effects. Penile curvature was measured from photographs taken in the outpatient clinic during full erections induced by intracavernosal PGE1 (69 patients) or with trimix (six), as 62 of the 75 patients (83%) had erectile failure of various degrees and thus autophotography was considered unreliable [4]. The present follow-up was deliberately short, to separate drug-related improvements from spontaneous changes in disease severity. Occasional spontaneous resolution of Peyronie's disease has been reported but only over several years, so short-term variations in disease severity should help to distinguish the effects of drugs from spontaneous change [14].

Qualitative data (pain reduction, disease progression, need for surgery and side-effects) were assessed using the chi-squared test; as pain was measured using an international pain scale, ANOVA was considered inappropriate [8], the scale comprising only four steps. Quantitative data were compared using ANOVA, in a 2×2 factorial analysis in the double-blind controlled study, as the number of patients was equal in the two groups, thus avoiding individual confounding, and in the prospective study, where randomized block analysis was used [8].

The double-blind trial showed that PLC and verapamil significantly reduced plaque size, penile curvature and

BJU International 77121-40 7/3/02 18:24:49 Rev 7.51a/W (May 2 2001)
The Charlesworth Group, Huddersfield 01484 517077

EDV, and significantly increased the IIEF score and RI, while tamoxifen and verapamil did not. PLC and verapamil were significantly more effective than tamoxifen and verapamil in preventing disease progression and the need for surgery. PLC and verapamil caused significantly fewer side-effects than tamoxifen and verapamil, but there were no significant differences between the groups in pain reduction. No drug association affected the PSV. Tamoxifen and verapamil seemed to be inactive on the quantitative variables, preventing progression in 80% of patients, similar to the rate reported previously [4] (but significantly lower than PLC and verapamil), while untreated Peyronie's has a 90% progression rate [4]. The ANOVA includes data from the whole group using tamoxifen and verapamil, which includes data from patients whose disease ameliorated, stabilized or progressed, thus inducing the false idea that tamoxifen and verapamil is inactive.

The prospective study confirmed the high activity of PLC and verapamil, which was effective in 14 of 15 patients with progressive disease. Thus, even though specific trials are needed, the present approach might provide the gold standard therapy for Peyronie's disease.

Dynamic colour Doppler scanning of the cavernosal arteries, with the increased IIEF score, showed that PLC and verapamil reduced the EDV and increased the RI, thus confirming that most erectile failure associated with Peyronie's disease is caused by venous leakage; indeed, there was no activity on the PSV [4].

Tamoxifen has confirmed anti-fibrotic activity in retroperitoneal fibrosis [15]; it decreased the expression of TGFβ1 [16], which up-regulates fibroblast proliferation and collagen synthesis [17]. TGFβ1 also down-regulates fibrosis, i.e. the final pathway of inflammation. Verapamil inhibits calcium deposition [18], proteoglycan synthesis [19], immune response, T cell motility [20], leukocyte migration and activation [21], and down-regulates inflammation, fibrosis and cellular mechanisms of immune response. PLC protects and restores cells with damage caused by inflammation [2,3] and ischaemia [22], and down-regulates most inflammation agents and up-regulates aerobic metabolism [1,5]. Biochemically, PLC and verapamil provide a more complete anti-inflammatory combination than tamoxifen and verapamil. Thus the combination of intraplaque verapamil, oral PLC and oral tamoxifen might be interesting.

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Abbreviations: , propionyl-L-carnitine; , International Index of Erectile Function; , peak systolic velocity; , end-diastolic velocity; , resistivity index.

BJU International 77121-40 7/3/02 18:24:50 Rev 7.51a/W (May 2 2001)
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