

Calcium Dobesilate for the Treatment of Erectile Dysfunction in Men with Diabetes Mellitus

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Abstract: Calcium dobesilate has shown to improve endothelial function. This proof-of-concept clinical trial was done to check whether it may improve erectile dysfunction in diabetic men. Male diabetic patients with a diagnosis of erectile dysfunction were randomized to receive either calcium dobesilate 1 g twice per day or placebo for 6 weeks. The International Index of Erectile Function (IIEF) was chosen as the primary efficacy measurement. Statistical procedures included a pre-scheduled adaptive interim analysis to recalculate sample size. Relevant, but not significant differences in the mean change from baseline in the primary end-point (IIEF questions 3, 4 and 7) favouring dobesilate with respect to placebo were observed. Such differences reached statistical significance in some secondary end-points, including IIEF global as well as the erectile function and intercourse satisfaction domains' scores. Some patients experienced an important placebo effect. Results suggest that dobesilate may be of help to treat diabetic erectile dysfunction. Co-administration with phosphodiesterase inhibitors warrants further investigation.

The relaxation of arterial and trabecular penile smooth muscle is needed to achieve and maintain penile erection [1]. Penile smooth muscle tone is under the control of relaxing and contractile mediators that are released from autonomic nerve terminals and the endothelia of corpora cavernosa lacunar spaces and penile arteries. The endothelium seems to play a crucial role in facilitating the erectile response. In fact, in ageing and vascular diseases associated with endothelial dysfunction such as hypercholesterolaemia and hypertension, a high prevalence of erectile dysfunction is also observed [2]. Diabetes is associated with endothelial dysfunction [3,4], as well as with a high incidence of erectile dysfunction [5].

Nitric oxide is a key mediator of endothelium-dependent relaxation. However, the existence of an unidentified endothelial factor that promotes smooth muscle hyperpolarization and relaxation and is resistant to nitric oxide synthase and cyclooxygenase inhibition has been clearly established, which has particular functional relevance in small arteries [6,7]. We have recently demonstrated that, while in human corpus cavernosum endothelium-dependent relaxation is mediated by nitric oxide, in human penile resistance arteries, in addition to nitric oxide, the endothelium-derived hyperpolarizing factor (EDHF) contributes significantly to endothelium-dependent relaxation [8]. In patients, in several

vascular beds, it has been shown that diabetes impairs endothelium-dependent relaxation mediated by nitric oxide [3,4,9], including human corpus cavernosum [10]. The effects of diabetes on EDHF-mediated responses in human vasculature have been less studied, but we have recently reported that EDHF-mediated relaxation is impaired in penile resistance arteries from diabetic patients with erectile dysfunction [11].

Calcium dobesilate has been extensively used as an orally administered angioprotective agent, especially in the treatment of diabetic retinopathy [12]. Although its mechanism of action is poorly understood, this compound has been shown to enhance endothelium-dependent relaxation of aorta in rabbits [13] and diabetic rats [14], as well as to improve endothelial function in diabetic patients [12]. This could be related to the *in vitro* capacity of increasing endothelial nitric oxide synthase activity by magnesium dobesilate [15]. Furthermore, we have previously reported that calcium dobesilate potentiates endothelium-dependent relaxation of human penile arteries by specifically enhancing the responses mediated by EDHF [8], and it was able to recover EDHF-mediated dilation of penile arteries from diabetic patients with erectile dysfunction [11]. In addition, calcium dobesilate has been reported to act as an antioxidant both *in vitro* [16] and *in vivo* [17]. This ability could be especially relevant in diabetic erectile dysfunction, because oxidative stress plays a significant role in the pathogenesis of diabetes-associated endothelial dysfunction [18]. In fact, the treatment with the antioxidants α -lipoic acid and vitamin E has been shown to enhance *in vitro* nitric oxide-mediated relaxation of corpus cavernosum from diabetic rats and

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mice, respectively [19,20], and treatment with vitamin E has also been reported to improve erectile responses in diabetic rats [21]. Taken together, these actions, the enhancement of nitric oxide and EDHF, as well as the scavenging of oxidants, target the endothelial dysfunction associated to diabetes. Because in diabetic patients systemic erectile dysfunction is strongly associated with erectile dysfunction [22,23], dobesilate could have a positive impact on erectile function of diabetic patients.

Type 5 phosphodiesterase (PDE5) inhibitors, which enhance nitric oxide/cyclic guanosine 3',5'-monophosphate relaxant pathway, are standard treatments for erectile dysfunction, although their efficacy has been reported to be lower in diabetic patients compared to general population [24–26]. In our hands, the administration of the PDE5 inhibitor sildenafil did not restore erectile function in diabetic rats, while the combined administration of sildenafil and dobesilate completely reversed erectile dysfunction in these animals [27]. These facts open the avenue of new therapies to improve the efficacy of the treatment for erectile dysfunction in diabetic patients.

With these premises, a proof-of-concept clinical trial to evaluate calcium dobesilate for the treatment of erectile dysfunction in diabetic patients was performed. The aim of this article is to communicate the results of this clinical trial and to discuss the future perspectives of this new pharmacological approach based on these results.

Materials and Methods

Patient selection. Out-patient men aged between 18 and 75 years old suffering from erectile dysfunction (less than 50% successful attempts to reach and sustain an erection firm enough for intercourse for at least 3 months), with type I or II diabetes mellitus undergoing pharmacological treatment, with a sexually stable relationship, and being willing to accomplish a minimum of five attempts of sexual intercourse within the last week prior to the efficacy evaluations, were eligible for the study. In addition, prior to randomization, a pharmacostimulation test with Doppler evaluation 20 min. after an intracavernosal injection of PGE₁ ruled out patients with macrovascular disease (defined as a peak systolic velocity in the proximal portion of the cavernosal artery >25 cm/sec. and an end diastolic cavernous blood velocity <5 cm/sec.). Patients with moderate to severe hypertension, macroscopic vascular disorders of the penis or Peyronie's disease, neurological diseases, endocrine disorders other than diabetes, severe psychiatric diseases, or impaired renal function were excluded; as were men with pregnant partners, bearing penile prostheses or who had undergone prior radical prostatectomy. Treatments with β -blockers, diuretics, α -methyl DOPA, clonidine, reserpine, guanethidine or testosterone were forbidden during the study. Recruitment took place in five centres within the Czech Republic. The study protocol was reviewed by the local ethics committees concerned and approved by the Czech health authorities. The clinical trial was conducted in agreement with all local regulations, the Declaration of Helsinki and its updates and in accordance with Good Clinical Practice.

Treatments. After recruitment, participants were enrolled into a 2-week single-blind, placebo run-in period. At the end of the run-in period, qualifying patients were randomized to a 6-week double-blind treatment period with two parallel groups, placebo or calcium dobesilate 1 g twice a day.

Measurements. According to the proposal by the National Institutes of Health Consensus Development Conference Panel on Impotence, the concept of erectile dysfunction entails two functional components (inability to achieve and maintain an erection sufficient for intercourse) and one subjective component (satisfaction with sexual performance) [28,29]. In consequence, we defined the primary efficacy end-point for this study as the aggregate (sum) of the scores of the items 3 (regarding the ability to achieve an erection sufficient for intercourse), 4 (regarding the ability to maintain such erection sufficiently for intercourse), and 7 (regarding the degree of satisfaction achieved) of the International Index of Erectile Function (IIEF) [30]. Changes in the global and in five domains scores were used as secondary end-points. The questionnaire was administered before and after the 6-week double-blind treatment. In addition, some patients underwent a nocturnal penile tumescence and rigidity test by means of a RigiScan device (Dacomed Corp., Minneapolis, MN, USA) at the same time-points. The RigiScan plus software was used to calculate the tip tumescence and base rigidity activity units from each measurement. A Doppler sonography of the penile vasculature was also performed at the final visit.

Statistics. Although the investigational drug was marketed some decades ago, this was the first clinical experience for the indication of erectile dysfunction; thus, the information needed to perform a formal sample size calculation was not available at the planning step. As this was intended to be a proof-of-concept study to warrant further clinical research, a sequential two-stage procedure was followed. We followed the proposal by Bauer and Köhne based on Fisher's criterion using the product of the P-values [31]. This method permits a reassessment of the sample size at the time of the interim analysis preserving the global significance and power of the study.

Treatment groups were compared to test the null hypothesis of equal or less effects in the dobesilate group by means of a t-test using analysis of covariance of the least square means, considering the factors treatment and centre, and the baseline value as covariate. The intention to treat population was taken as the primary analysis population. A global 2.5% significance level was considered for all the comparisons; thus, according to Fisher's criterion, the null hypothesis could be rejected under a critical value of the product P-value of 0.0038 [31].

The results of the RigiScan assessments were analysed descriptively. Frequency tables were used to summarize adverse events.

Results

Patient population and disposition.

A total of 99 patients were recruited between March 2000 and July 2001. There were seven screening failures. Of the remaining 92 patients, 46 were randomly assigned to each group, and were all included in the safety population. One patient allocated to the dobesilate group failed to attend after the randomization visit and two patients allocated to the placebo group were excluded from the efficacy analyses, because they did not meet the inclusion criteria (although one of these was recruited in the first stage, he was excluded after the end of the trial and, therefore, his data were used for the calculation of the sample size at the interim analysis). Consequently, the intention to treat population comprised 89 patients, 44 and 45 in the placebo and dobesilate groups, respectively. Fifty-six were included during the first stage and the remaining 33 after performing the interim analyses. Glycosylated haemoglobin was below 6% in 22 out of 92 patients (23.9%) and above 9% in 13 (14.1%). The remaining

Table 1.

Baseline characteristics in the safety population.

	Dobesilate	Placebo	Total
Age, years (n/mean \pm S.D.)	46/57.72 \pm 8.49	46/56.33 \pm 9.80	92/57.02 \pm 9.14
Weight, kg (n/mean \pm S.D.)	46/89.49 \pm 11.90	46/84.00 \pm 10.0	92/86.75 \pm 11.27
Height, cm (n/mean \pm S.D.)	46/179.08 \pm 6.70	46/176.96 \pm 6.68	92/178.02 \pm 6.74
Time since onset of diabetes, years (n/mean \pm S.D.)	46/7.54 \pm 6.11	46/9.46 \pm 8.06	92/8.50 \pm 7.18
Toxic habits – tobacco, cigarettes per day (number of smokers/mean \pm S.D.)	10/4.30 \pm 2.98	7/5.60 \pm 3.10	17/4.82 \pm 3.00
Toxic habits – alcohol, grams per day (number of drinkers/mean \pm S.D.)	7/14.29 \pm 10.18	6/15.00 \pm 18.71	13/14.62 \pm 14.06
Severity of erectile dysfunction			
Mild (erectile function subscale score \geq 18) (n/%)	10/21.74	8/17.39	18/19.57
Moderate (erectile function subscale score \geq 11 and $<$ 18) (n/%)	27/58.70	29/63.04	56/60.87
Severe (erectile dysfunction subscale domain $<$ 11) (n/%)	9/19.57	9/19.57	18/19.57

57 (62.0%) had values in-between. Other baseline characteristics were comparable between both groups (table 1).

Efficacy.

Because of the statistical procedure employed, P-values expressed are the result of the product of the individual P-values from both stages of the trial.

Relevant differences in the least square mean change of the sum of the scores to the IIEF questions 3 (ability to achieve erection), 4 (ability to maintain erection), and 7 (degree of satisfaction achieved) favouring calcium dobesilate with respect to placebo were observed in the first stage (2.14 versus 1.07, respectively, one-sided P-value = 0.0087), but not at the second (1.64 versus 1.71, respectively, one-sided P-value = 0.5505). Global significance is given by the product of those P-values, that is, 0.0044. Although the latter value neighbours the critical value of 0.0038 to reject the null hypothesis of equal or less effects with dobesilate than with

placebo, it is not underneath. For the whole sample, the 95% confidence interval for the adjusted mean response in the calcium dobesilate group was 1.45 to 2.60, while that for the placebo group was 0.84 to 1.98 (table 2; fig. 1); the overlap between them confirms the absence of significant differences. In addition, in the whole sample, the 95% confidence interval for the difference between groups (calcium dobesilate effect minus placebo effect) was -0.08 to 1.31; being the point estimate 0.61 points (fig. 1). Consistently, it favours calcium dobesilate, but contains the origin (0) by a thin margin.

Secondary end-points also showed a greater benefit with calcium dobesilate than with placebo. Furthermore, the differences reached statistical significance in some of them. Such was the case with the global score of the IIEF (least square mean change with calcium dobesilate and placebo: 10.53 and 7.01 points, respectively; one-sided product P-value = 0.0004); as well as with the scores of the erectile function (3.91 and 2.65 points, one-sided product

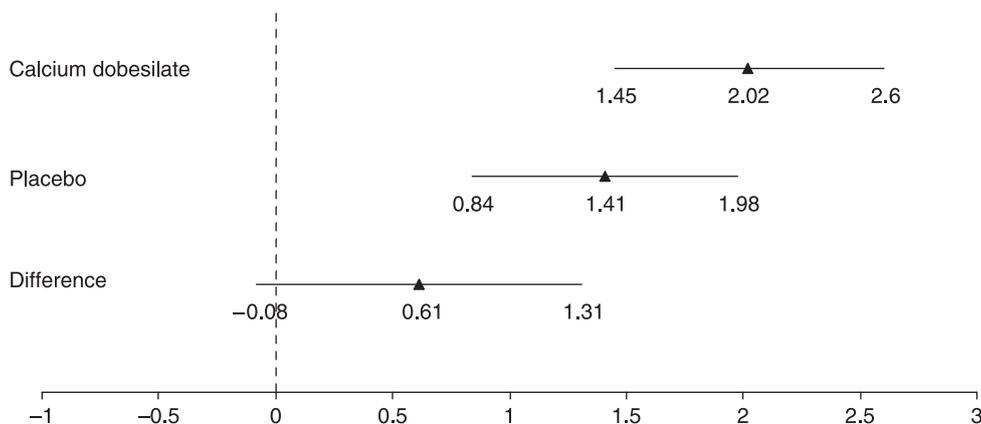


Fig. 1. Ninety-five per cent confidence intervals for the adjusted mean responses as determined by means of the primary efficacy end-point (change from baseline in the primary efficacy end-point – sum of scores of items 3, 4 and 7 of the International Index of Erectile Function) within each treatment group. The difference was calculated as the change from baseline attained with calcium dobesilate minus the change attained with placebo. Positive figures indicate more benefit with calcium dobesilate. A confidence interval lying entirely over the origin (0) would indicate statistical significant differences favouring calcium dobesilate.

Table 2.

Effects of the treatments on the scores of the International Index of Erectile Function (IIEF). Intention to treat population. Treatments were calcium dobesilate 2 g/day or placebo for 6 weeks.

	Mean scores								Difference between treatments	
	Placebo (n = 44)				Calcium dobesilate (n = 45)				Diff. CI	Product P-value ¹
	Pre [mean (S.D.)]	Post [mean (S.D.)]	Change [LSM (S.E.M.)]	Change CI	Pre [mean (S.D.)]	Post [mean (S.D.)]	Change [LSM (S.E.M.)]	Change CI		
Primary end-point (sum of scores to items 3, 4 and 7; range 0–15)	7.93 (2.79)	9.14 (2.99)	1.41 (0.29)	0.84–1.98	7.27 (2.25)	9.18 (2.77)	2.02 (0.29)	1.45–2.60	–0.08–1.31	0.0048
Global score (sum of scores to all items; range 5–75)	38.14 (10.28)	44.93 (11.96)	7.01 (1.29)	4.45–9.57	36.62 (7.84)	47.29 (11.32)	10.53 (1.29)	7.98–13.09	0.41–6.63	0.0004 ¹
Erectile function (sum of scores to items 1–5, 15; range 1–30)	14.50 (4.76)	17.07 (5.79)	2.65 (0.61)	1.43–3.86	14.24 (3.71)	18.16 (5.38)	3.91 (0.61)	2.71–5.12	–0.19–2.73	0.0008 ¹
Intercourse satisfaction (sum of scores to items 6–8; range 0–15)	7.64 (2.54)	9.36 (2.22)	2.09 (0.25)	1.60–2.59	6.84 (2.04)	9.51 (2.07)	2.70 (2.25)	2.20–3.20	0.00–1.21	0.0010 ¹
Orgasmic function (sum of scores to items 9–10; range 0–10)	5.86 (2.52)	6.45 (2.35)	0.62 (0.26)	0.10–1.14	5.71 (2.28)	6.87 (2.19)	1.13 (0.62)	0.61–1.64	–0.12–1.14	0.0121
Overall satisfaction (sum of scores to items 13–14; range 2–10)	4.41 (1.81)	5.66 (2.15)	1.16 (0.29)	0.59–1.72	4.16 (1.41)	6.02 (2.19)	1.67 (0.28)	1.11–2.23	–0.18–1.20	0.0077
Sexual desire (sum of scores to items 11–12; range 2–10)	5.73 (1.59)	6.39 (1.51)	0.57 (0.21)	0.16–0.98	5.67 (1.65)	6.73 (1.71)	0.93 (0.21)	0.52–1.34	–0.14–0.86	0.0172

Pre, before treatment, baseline; post, after treatment; change, adjusted mean [least square mean (LSM)] of the pre- to post-treatment changes in the scores of each patient; change CI, 95% confidence interval for the adjusted mean response within each treatment group; diff. CI, 95% confidence interval for the difference in adjusted mean responses between both treatment groups; product P-value, product of the error probabilities for the tests in both subsamples for the rejection of the null hypothesis of less or equal response in the dobesilate group; S.D., standard deviation; S.E.M., standard error of the mean; LSM, least square mean.

¹Significant differences between the groups (the critical value for the product P-value is 0.0038, instead of 0.025, see ‘Statistics’ in the text).

Table 3.

Results of the nocturnal penile tumescence test after processing with the RigiScan Plus software. Summary of measurements from two consecutive nights. Results are expressed as number of evaluations/mean \pm S.D.

	Placebo			Calcium dobesilate		
	Pre	Post	Mean change	Pre	Post	Mean change
Tip tumescence activity units	8/5.25 \pm 4.83	7/4.57 \pm 5.77	7/-1.14 \pm 3.44	10/6.70 \pm 6.46	9/8.00 \pm 6.10	9/0.89 \pm 6.58
Base rigidity activity units	8/9.25 \pm 8.45	7/6.00 \pm 6.53	7/-4.29 \pm 7.32	10/15.50 \pm 13.91	9/16.22 \pm 15.63	9/-0.11 \pm 21.41

Pre, before treatment; post, after treatment; mean change, mean of the pre- to post-treatment changes in the scores of each patient.

P-value = 0.0010) and intercourse satisfaction (2.70 and 2.09 points, one-sided product P-value = 0.0035) domains. Complete results related to IIEF are summarized in table 2.

The nocturnal penile tumescence and rigidity testing was performed in 16 patients, nine of whom were assigned to calcium dobesilate and seven to placebo. There were not relevant changes from baseline in any of the groups, but a trend was observed towards a slight increase in the tip tumescence with calcium dobesilate. The combined results from both stages on base rigidity and tip tumescence activity are summarized in table 3.

The Doppler ultrasonography of the penile vasculature performed at the end of study visit did not show changes with respect to that performed prior to the intracavernosal injection of PGE₁ at the randomization visit (data not shown).

A further multifactorial analysis of covariance performed over the whole sample of the study, including the severity of diabetes and of the erectile dysfunction as new factors, was performed to explore their influence over the response. Neither of these was significant (data not shown).

Treatment was very well-tolerated. In the group of calcium dobesilate, only two adverse events (diarrhoea and increase of hepatic enzymes) were reported. Both were rated as moderate in intensity and were not considered related to the study medication by the investigator. In the placebo group, seven adverse events were reported (sweating, hyperprolactinaemia, gingivitis, increase of hepatic enzymes, anaemia, and respiratory tract infections in two patients). All were rated as of mild intensity and the investigators did not consider them to be related to the study medication. Neither severe nor serious adverse events were reported.

Discussion

Efficacy results in terms of the IIEF scores favoured calcium dobesilate over placebo. Nevertheless, the differences did not reach statistical significance. It has been reported how for the primary efficacy end-points the differences between treatments occurred in the first stage but not in the second. This occurred also with all IIEF-related end-points. This inconsistency is attributable to the divergence of the results in the placebo group between both stages of the study, as the effects attained with calcium dobesilate remained constant.

Whether a classical approach would have been employed with a sample size of 89 patients, the global sample size comprising the full analysis set in this clinical trial, a P-value of 0.0413 (calculated in an exploratory fashion) would have been obtained for the null hypothesis testing. Consistently with our results, at a 2.5% significance level, rejection would have not been possible. In fact, for detecting a difference between treatments of one point in the score of the primary efficacy end-point (which observed during the first stage), we would have needed at least 100 patients, assuming the standard deviation observed.

The predominance of the psychogenic component of the disease in this latter stage may have biased the study. To accelerate recruitment, advertisements were included in newspapers. While patients recruited before the interim analysis were well known by the investigators (most of them were derived by diabetologists working in the same centres than the investigators and had a long history of their diabetes recorded in the hospital files), those recruited after the adaptation came chiefly from other areas and the screening visit was the first time that attended to the study doctors' desk. The control of the sexual activities imposed by the study may have increased the expectations of patients favouring a good response to placebo. We did not collect precise information about the diabetes type. However, according to the epidemiology of the disease, it is expectable that most (or all) of the patients recruited had type 2 diabetes, which accounts for 90–95% of those with diabetes [32]. Rather than type, other factors, such as time since disease onset, the presence of other complications and, especially, glycaemic control, have been shown to determine the risk of erectile dysfunction [22,33,34], and these did not differ significantly between groups in this study. Thus, we do not expect that this unawareness is of relevance in the interpretation of the results.

While the placebo effect in this study was particularly higher than that reported in prior placebo-controlled studies of sildenafil, also the efficacy of calcium dobesilate was lower than that of the phosphodiesterase inhibitor [24–26]. Therefore, an insufficient effect by calcium dobesilate in the present study may have also account to the lack of a clear result. Based on the functional differences between penile arterial and trabecular tissues regarding responses to vasoactive stimuli [35], the incomplete efficacy of sildenafil in diabetic erectile dysfunction has been attributed to its

inability to enhance EDHF-mediated relaxations [11]. In this way, dobesilate alone might be only partially effective as well, but in this case, because it is not able to modify endothelium-dependent relaxing responses in corpus cavernosum despite its ability to enhance endothelial relaxation of penile arteries from diabetic and non-diabetic men [8,11].

A recent investigation that studied the effects of calcium dobesilate and sildenafil in diabetic rats has shown complete restoration of erectile function only when both compounds were given in combination, while each separately failed to significantly enhance erectile responses [27]. In a current context in which progressive and combined treatments for erectile dysfunction in diabetes mellitus have been considered [36], we propose calcium dobesilate as a potential therapeutic agent in future research.

Briefly, this study has a number of limitations. Implications of its smaller sample size have been addressed beforehand. In addition, it has been mentioned how the recruitment strategies may have favoured the selection of patients with relevant psychogenic components especially during the second stage and the impact that this may have had on results. Finally, the 6-week duration of treatment may seem short in the current context in which chronic treatments with phosphodiesterase inhibitors are being investigated for patients failing prior on-demand regimens.

In conclusion, this is, to our knowledge, the first report of the clinical effects of dobesilate over erectile dysfunction in diabetic men. Albeit modest, these results taken together with the pre-clinical data suggest that combining dobesilate with phosphodiesterase inhibitors could provide an additional benefit for these patients. A specific proof-of-concept study to address this issue is warranted.

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