Acceptability, efficacy and safety of two pharmaceuticals forms of diosmin 600 mg in patients with chronic venous disease: a randomised comparative multicenter study

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Abstract

Aim: To compare the acceptability, efficacy and safety of two pharmaceutical forms of diosmin 600 mg (Laboratoires Innothera) in patients with chronic venous disease.

Methods: Randomised comparative multicenter, phase IV study in general medicine. 1422 patients (average age: 53.4 years old, women: 89.1%) were included in the study and randomised into two intent-to-treat groups: 722 patients receiving the tablet and 720 patients the sachet of powder for oral suspension of diosmin 600 mg. The treatment was administered in single daily dose (in the morning) for 28 days. The acceptability as well as the pain intensity were evaluated by the patients using visual analogue scales (VAS) before and after treatment. A three-level scale (absence, moderate and severe) was used to evaluate other venous symptoms that could be present at all CEAP stages of CVD.

Results: The overall efficacy of the two pharmaceutical forms, as evaluated by the doctors, is good to very good for 91 % of patients. Pain (experienced by 97 % of the patients at inclusion) was significantly reduced after treatment ($p<0.0001$), with no difference between the two pharmaceutical forms ($p=0.45$). All other clinical signs (heavy legs, evening oedema, paraesthesia, cramps, restlessness of lower limbs, pruritus) reported at inclusion, had disappeared or were less intense ($p<0.0001$) at the end of the trial. This clinical improvement had a positive influence on patients' day-to-day activities. Lastly, the two pharmaceutical forms, tablet and sachet, were well accepted by respectively 86 % and 83 % patients and very well tolerated (99 %), explaining the excellent compliance to treatment (96 %).

Conclusion: The study confirms the efficacy of diosmin 600 mg once a day in improving all symptoms of chronic venous disease. The results highlight good acceptability and safety of the two pharmaceutical forms, tablet and sachet, with comparable efficacy on venous symptoms.

Key words: Chronic venous disease, diosmin, pharmaceutical form, acceptability, efficacy, safety, compliance.

Introduction

Chronic venous disease (CVD) is a very widespread disorder. According to Lévy et al. (1), half of France's population experiences CVD symptoms and 43 % of these persons go untreated. Similar results are found in most of the epidemiological studies that are carried out in industrial countries. According to a recent assessment made by Meissner et al. of three epidemiological studies conducted in Germany, Poland and France, the prevalence of the least serious manifestations of CVD (C0-C3) of the CEAP clinical classification stands at 50 % (2-5). As it is responsible for morbidity and alters quality of life, CVD can lead to significant socio-economic repercussions in terms of consultations, medical treatment or surgical intervention (6). It is a chronic, progressive disease and early management is desirable in order to avoid or at least slow down its progression towards more serious forms. Indeed, patients often start their treatment years after the onset of symptoms.

Venous symptoms can be present at all stages of venous disease: "venous pain" might be the element that triggers medical consultation in initial stages of the

disease. Phlebotonics have proven to be effective on the clinical signs of CVD and improve patients' quality of life (7). Diosmin 600 mg (Laboratoires Innothera), has the advantage of requiring only one tablet per day. Its pharmacological properties are well established. It has vasculoprotective and anti-inflammatory action, (8-11), and its phlebotonic effect (controlled by plethysmography) has been documented in the Barbe et *al.* study (11). Its fast (from the 2nd hour) and prolonged action (up to 20 hours), as highlighted in this clinical pharmacology study, justifies a once-daily administration. The clinical efficacy and safety of diosmin have been widely studied and proven (12-16).

The aim of this multicenter study in general practice is to compare the acceptability, efficacy and safety of two pharmaceutical forms of diosmin 600 mg (Laboratoires Innothera): the tablet and the powder for oral suspension (sachet), in patients with chronic venous disease of the lower limbs.

Patients and Methods

The protocol of this multicenter phase IV study received approval from the Ethics Committee (CCPPRB) of the Hôpital Boucicaut, Paris-France. All the patients included in the study were informed of the objectives and the restrictions of the trial and signed to indicate their informed consent. They were randomised into two groups at the outset of the trial (D0): one group receiving one tablet per day and the other group one sachet per day of diosmin 600 mg, for 28 days.

The patients included were men and women presenting suggestive symptomatology of CVD (leg pain, feeling of heavy legs, restless leg syndrome disrupting sleep), and who can benefit from a treatment by phlebotonic. In order to evaluate the acceptability and efficacy of diosmin 600 mg in general practice, the trial did not entail any specific criteria for inclusion with the product used under the conditions set by the Marketing Authorisation. Any prior phlebotonic treatment was stopped upon inclusion in the trial. On the other hand, if the patient was using a medical compression device, this was maintained throughout the duration of the study.

The doctor performed clinical exams on D0 and D28. The acceptability of the treatment was determined by means of a visual analogue scale (VAS) running from 0 mm (very badly accepted) to 100 mm (very well accepted).

The efficacy of the treatment was evaluated by comparing the intensity of the venous symptoms before and after treatment. Patients quantified venous pain using a VAS running from 0 mm (no pain) to 100 mm (severe pain). Every clinical symptom characteristic of CVD (feeling of heavy legs, evening oedema, paraesthesia, night-time cramps, pruritus and restlessness of the lower limbs) was evaluated using a three-level scale. Furthermore, the impact of CVD on patients' activity was assessed using simple questions (yes or no answers). Lastly, the doctors evaluated the patients' evolution at the end of treatment in order to judge the overall efficacy of diosmin 600 mg.

Compliance to treatment was estimated by the amount of products that remained in boxes returned at the end of the trial. The investigator gathered information about adverse effects during an interview.

The CEAP classification was not adopted in this study conducted in general medicine, but the clinical description is based on the existence of the following clinical signs: telangiectasia, varicose veins, oedema and trophic disorders. All the patients included in the trial presented some of these symptoms.

Comparisons between the pharmaceutical forms (intergroup comparisons) were conducted by means of a Student's t-test or a non-parametric Mann-Whitney test (if the Student's t-test is invalid) for the quantitative or semi-quantitative variables, and by means of a Chi-square test or Fisher's exact test for the qualitative variables. The comparisons between the two consultations (intragroup comparisons) were carried out using a Student's t-test on paired series or a non-parametric Wilcoxon test (in the event that the Student's t-test is invalid) for the quantitative or semi-quantitative variables, and using a McNemar's test on paired series for the qualitative variables. The statistical significance threshold was set at 0.05.

Results

In total, 750 centers recruited 1546 patients. There was no data available on 46 patients (lost-to-follow-up) after inclusion, they were excluded from all the tests. Safety was evaluated on the entire population monitored (n=1500) and the efficacy on the intent-to-treat (ITT) population. That last includes 1442 patients who consumed at least once the tested treatment whose prescribed form is known and validated and for whom at least one piece of data on efficacy or acceptability has been provided. The ITT population was divided as follows: 722 into the "tablet" group and 720 into the "sachet" group.

1. Description of the population

The main demographic data, clinical data and data relating to the history of the disease on the 1442 patients forming the ITT population is shown in Tables I to III and in Figure 1.

This data is particularly informative as it allows for a better interpretation of the results (Tables I and II). The proportion of women (89.1 %) is much higher than in the epidemiological studies and reflects the earlier treatment of women who become aware of their "vein disorders"

Table I: Demographic data

		Tablet (n=722)	Sachet (n=720)	Total (n=1442)
Gender	Women: n (%)	638 (88.4%)	647 (89.9%)	1285 (89.1%)
	Men: n (%)	84 (11.6%)	73 (10.1%)	157 (10.9%)
Age (years)	M ± SD	53.9 ±14.5	53.0 ± 14.9	53.4 ± 14.8
Weight (kg)	M ± SD	67.9 ±13.7	66.9 ± 12.6	67.4 ± 13.2
BMI (kg/m²) :	M ± SD	25.1 ± 4.8	24.9 ± 4.5	25.0 ± 4.7
n: number of patients ; M ± SD: mean ± standard deviation; BMI: Body Mass Index.				

Table II: History of the disease and work-related restrictions

	Tablet (n=722)	Sachet (n=720)	Total (n=1442)
History of the disease			
Time to onset (years): M ± SD	10.1 ± 9.0	10.3 ± 9.6	10.2 ± 9.3
Previous consultation: n (%)	564 (78.2 %)	564 (78.6 %)	1128 (78.4 %)
Prior use of phlebotonics*: n (%)	523 (73.5 %)	512 (71.7 %)	1035 (72.6 %)
Prior use of compression†: n (%)	134 (18.8 %)	189 (26.7 %)	323 (22.8 %)
Work-related restrictions			
Prolonged standing: n (%)	198 (31.7 %)	222 (36.0 %)	420 (33.8 %)
Prolonged sitting: n (%)	209 (33.9 %)	181 (29.5 %)	390 (31.7 %)
Airplane travel: n (%)	20 (3.3%)	17 (2.9%)	37 (3.1%)
M ± SD: mean ± standard deviation ; n: number of patients *Time between treatment stop and the study inclusion visit: 272 ± 624.9 days; † support stockings : 70 % ; compressive stockings : 30 %			

Table III: Description of the population based on the results of the clinical exam

Clinical exam	Tablet (n=722)	Sachet (n=720)	Total (n=1442)
Telangiectasia	79.4 %	76.3 %	77.9 %
Varicose veins	70.3 %	69.9 %	70.1 %
Oedema	51.1 %	46.5 %	48.8 %
Trophic disorders	22.5 %	21.6 %	22.1 %

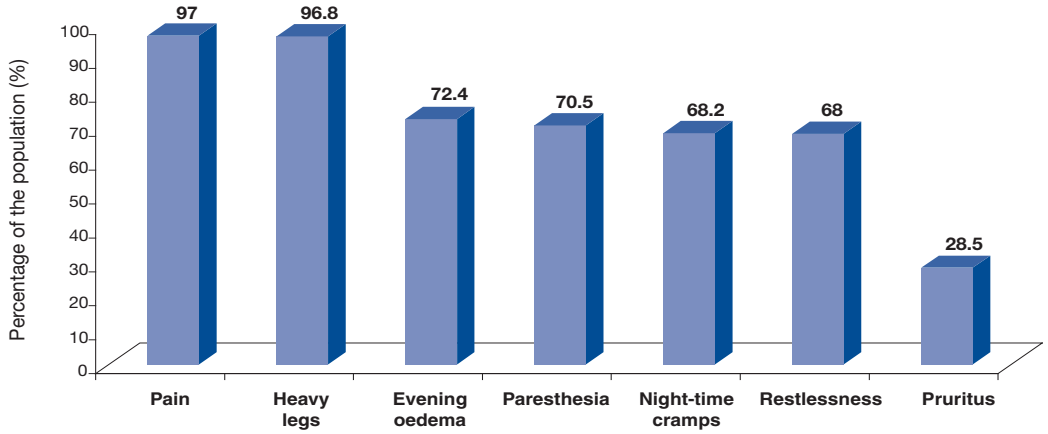

Figure 1: Frequency of different chronic venous disease symptoms at inclusion

sooner than men. Given the average age of the patients included (53.4 years old) and bearing in mind that age is a risk factor in the development of CVD, it is not surprising to see that the first venous symptoms appeared on average 10.2 years beforehand. The very early presence of venous symptoms also explains the fact that at the beginning of the trial, 78.4 % of patients had already consulted a doctor about their CVD, 72.6 % of patients had already been treated with phlebotonics and that 22.8 % wore items of compression clothing (70 % wore a support stocking and 30 % wore a compressive stocking). Among the factors that favour CVD, and more specifically the functional signs of CVD, prolonged standing was found with 420 patients and prolonged sitting was found with 390 patients. Lastly, recent airplane travel was a factor for 37 patients.

At the inclusion of the study, all the patients experienced pain as well as other venous symptoms. Figure 1 illustrates the frequency at inclusion of these symptoms. Pain and the feeling of "heavy legs" are the most frequently reported symptoms (97 % and 96.8 %) followed by evening oedema (72.4 %), paraesthesia (70.5 %), night-time cramps (68.2 %), restlessness (68 %) and pruritus (28.6 %). 59.7 % of patients stated that these clinical signs had a negative impact on their day-to-day activities.

2. Acceptability

The average acceptability on the VAS was 86.1 ± 15.2 mm for the tablet and 83.1 ± 17.3 mm for the sachet, showing that both forms were well accepted to a comparable degree in the two groups.

3. Efficacy according to the patient

The results concerning the efficacy of diosmin 600 mg combine the data obtained for the "tablet" group and for the "sachet" group, given that there was no difference observed between these two pharmaceutical forms.

3.1. Efficacy on pain

Table IV shows the evolution of pain intensity, measured using the VAS before and after treatment, for each and for both pharmaceutical forms.

At inclusion, 97 % of patients complained about lower limbs pain, making pain the most commonly clinical symptom reported in this study.

The pain intensity decrease was statistically significant after treatment in each group: -29.9 ± 20.0 mm in the "tablet" group, - 30.7 ± 19.8 mm in the "sachet" group and - 30.3 ± 19.9 mm for the total population (Student's t-test for paired series: p<0.0001), which made thus a 56.1 % pain intensity decrease. On the other hand, there was no significant difference between the two groups (p=0.45) (Figure 2).

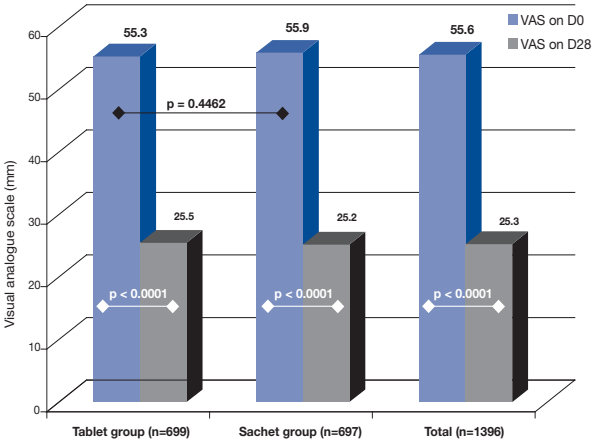

Figure 2: Reduction of lower limb pain on the visual analogue scale (VAS D0 and VAS D28)

Table IV: Evaluation of pain by a visual analogue scale running from 0 mm (no pain) to 100 mm (severe pain) on D0 and D28 and evolution of the pain (D0-D28)

		D0: (M ± ET)	D28 : (M ± ET)	Evolution (D0 - D28) : (M ± SD)	Percentage of variation (median) (%)
All patients	Total (n=1396)	55.63 ± 19.27	25.35 ± 16.76	-30.29 ± 19.89	- 56.1 %
	Tablet (n=699)	55.36 ± 19.23	25.48 ± 16.43	-29.88 ±20.00	- 55.6 %
	Sachet (n=697)	55.91 ± 19.32	25.22 ± 17.09	-30.69 ± 19.78	- 57.5 %
Patients with VAS ≥ 50mm at D0	Total (n=922)	67.07 ± 9.91	29.44 ± 16.73	-37.63 ± 18.08	- 57.9 %
	Tablet (n=456)	66.96 ± 10.15	29.61 ± 16.20	-37.34 ± 17.84	- 56.4 %
	Sachet (n=466)	67.19 ± 9.67	29.28 ± 17.25	-37.90 ± 18.33	- 59.0 %
M ± SD: mean and standard deviation					

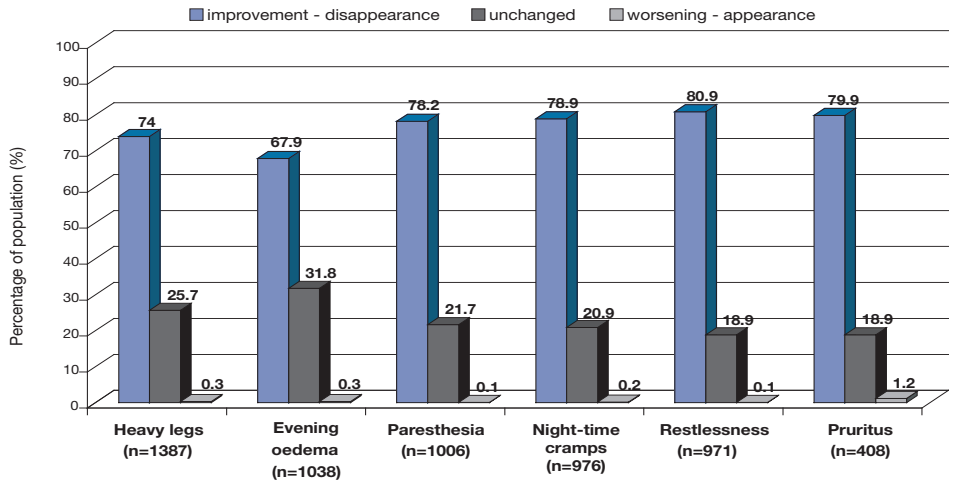

Figure 3: Evolution of symptoms experienced at the inclusion

In order to estimate the putative influence of pain intensity on the efficacy of the treatment, patients with a score ≥50 mm on the VAS at the inclusion of the study (n=922) were evaluated separately. The reduction in the intensity of the pain felt by patients was higher than for the whole ITT population, with -37.6 ± 18.1 mm and -30.3 ± 19.9 mm respectively.

3.2. Efficacy on other clinical symptoms and impact on day-to-day activities

Figure 3 shows the evolution reported for each clinical symptom of CVD. A significant improvement was observed for all the symptoms. The impact on day-to-day activities was reduced or was no longer felt for 71.5% of patients (Table V).

Table V: Evolution of the impact of the clinical symptoms on day-to-day activities

Evolution	Total	
	n	%
Improvement or disappearance	613	71,5
No change	244	28,5
Total	857	100,0

4. Efficacy according to the doctor

Table VI shows the results of the overall evolution of venous disorders according to the doctor. Analysis of the results confirms the strong improvement or average of CVD symptoms among 91.7% of patients in the "tablet" group and 91.4% of patients in the "sachet" group with no significant difference between the two groups (p>0.05).

5. Compliance and Safety

Compliance was very high in both groups with 95.9 ± 14.1 % in the "tablet" group and 96.5 ± 14.7 % in the "sachet" group.

The overall safety, evaluated on the safety population (n=1442), was judged as good by 99 % of patients in the "tablet" group and by 98.5 % of patients in the "sachet" group. Only 22 patients presented an adverse effect for which the responsibility of the treatment has not been excluded; they were digestion problems. Six patients (0.4 %) stopped the study prematurely due to an adverse effect. No serious adverse effect was reported.

Discussion

This trial confirms the efficacy of diosmin 600 mg on chronic venous disease symptoms, whether it is

Table VI: Overall judgement by doctors: Evolution of the symptoms in "tablet" and "sachet" groups

	Tablet (n=722)	Sachet (n=717)	Total (n=1439)
Strong improvement	42.8 %	41.6 %	42.2 %
Average improvement	48.9 %	49.8 %	49.3 %
No change	7.2 %	8.4 %	7.8 %
Slightly worse	0.6 %	0.3 %	0.4 %
Much worse	0.6 %	-	0.3 %

administered by tablet or by sachet of powder for oral suspension. No significant difference in the efficacy, compliance, safety and acceptability was observed between the two forms. The statistically significant reduction in pain, documented on the VAS, is around 60 %. This analgesic action is higher as the pain is intense at D0. A similar reduction was observed for all other functional signs. Finally, the acceptability and compliance are very good for both pharmaceutical forms, certainly in touch with the single daily dose and the good safety of diosmin 600 mg.

In conclusion, this study conducted by general practitioners on more than 1400 patients with chronic venous disease symptoms confirms the efficacy of diosmin 600 mg once a day on the functional signs of venous disease that can be present at all clinical stages of CEAP classification. The pharmaceutical form does not modify the efficacy of the treatment that remains optimum in tablet and sachet forms, thereby allowing the patient to choose the presentation that best suits him or her. The benefit/risk ratio is important due to efficacy on the major venous symptoms. The study shows the good acceptability and compliance in touch with the very good safety. This study confirms that diosmin 600 mg in a single daily dose is an safe and effective active substance to relieve CVD patients' complaints.

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