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Prevention of recurrent cystitis with GynDelta®

Results of a randomised, double-blind study

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Results of a randomised, double-blind study on the prevention of recurrent cystitis with GynDelta®

Dr Jean-Marc BOHBOT, A. Fournier Institute, Paris.

ABSTRACT

• Study objective

To investigate the impact of consuming cranberry capsules in a single, post-coital dose on the onset of lower tract urinary infections in female patients presenting with recurrent urinary infections.

• Methodology, location and participants

A prospective, randomised, double-blind study conducted over a period of 45 days between May and August 2006, at the A. Fournier Institute, (Paris), in 120 female patients having had over 6 lower urinary tract infections during the last 12 months. The patients were randomly allocated to one of three groups.

• Procedure

In the 6 hours following intercourse, each patient had to take a single dose of:

- **Either 1 capsule infused with cranberry powder according to the Bioshield procedure, (GynDelta®);**
- **Or 1 capsule of dry cranberry extract containing 36 mg of pro-anthocyanidins A (PAC);**
- **Or 1 placebo capsule (magnesium stearate and red iron oxide).**

• Evaluation criterion

Number of patients presenting with a recurrent episode of lower urinary tract infection.

• Results

Over the study period, 10.8% of patients in the GynDelta® group suffered a recurrent bout of lower urinary tract infection compared with 18.9% of patients in the cranberry group containing 36 mg PAC and 43.2% of patients in the placebo group.

• Conclusion

GynDelta® proved its efficacy in the prevention of lower urinary tract infections after a single, post-coital dose with a greater level of statistical significance (p = 0.005) than cranberry containing 36 mg of PAC (p = 0.048) compared with the placebo.

Lower urinary tract infection (LUI) is considered to be the most prevalent bacterial infection [1]. One in three women contracts LUI warranting treatment with antibiotics, before 24 years of age, and virtually one in two women will be affected by LUI during her lifetime [1]. Some categories of the population are more prone to this condition than others: the elderly, children, pregnant women, medullary trauma patients, diabetics, patients with a urinary catheter, immunosuppressed patients and patients with anatomical urinary tract anomalies, etc. are particularly at risk. LUIs are also common in subjects with no clearly identified risk factors and have a non-negligible risk of recurrence.

The prevention of recurring LUI has, until now, been based on the prolonged administration of antibiotics (over several months) with the risks of side affects and the development of resistance.

Ever since the studies of Sobota, in 1984 [2], we know that the cranberry *(Vaccinium macrocarpon:* the wild bilberry of North America) is likely to inhibit the adherence of *Escherichia coli* to the urinary epithelium. This action appears to be related to the presence of tannins (pro-anthocyanidins and anthocyanidins [3]), which inhibit the synthesis of E. *coli* pili *[4]* and bind competitively to the bacterial receptors of the urinary epithelium [5]. Possessing marked, anti-radical properties, cranberry tannins could also exhibit anti-inflammatory activity [6] promoting good urethro-vesical, mucous trophicity [7].

Several clinical trials have confirmed the preventive role of the cranberry in the prophylaxis of recurrent, urinary infections. This efficacy was validated in 2004 by a Cochrane library journal [8], which, nevertheless, specified that:

- The optimal dosage had yet to be defined;
- Problems of long-term compliance were noted with cranberry juice.

The same year, Afssa (Agence française de sécurité sanitaire des aliments – the French Agency for the Safety of Foodstuffs) authorised a health allegation on the basis of studies conducted by Avorn *et al*. [9] and Kontiokari *et al*. [10] stating, outside the conclusion, that 36 mg of pro-anthocyanidins were measured in one of these studies (Avorn).

Although this last study was not selected by Cochrane, we wished to compare the efficacy of two types of cranberry capsules versus placebo. The first capsule contained 500 mg of powder infused according to a patented procedure (Bioshield), allowing the entire berry to be conserved (GynDelta® in France), and the second was an extract of *Vaccinium macrocarpon* containing 36 mg of pro-anthocyanidins (PAC). The second objective was to assess the efficacy of cranberry consumption in accordance with a protocol to promote optimal compliance.

Sexual relations are very often incriminated as one of the causes of recurrence. According to certain studies, episodes of cystitis associated with sexual relations account for 4% of all LUIs and 60% of cases of recurrent cystitis [11]. One study showed that the risk of developing LUI was 2.6 times greater in a 24 year-old woman who had sexual relations within a 3-day period than in a woman of the same age who had not had intercourse for 8 days [12]. Amongst a student population, Strom *et al.* found a correlation between the proximity of sexual intercourse and the onset of cystitis with an odds ratio (OR) of 58 if intercourse had taken place less than 48 hours previously, and an OR of 9.1 when intercourse had been between 3 and 7 days earlier [13]. In 1995, Foxman *et al.* showed that even protected intercourse over the previous 15 days increased the risk of developing cystitis by 53% [14]. We, therefore, opted to assess the efficacy of a single, post-coital dose of cranberry (within 6 hours of sexual intercourse) in patients at high risk of recurrence.

Patients and methods

Between May and August 2006, 120 female patients between 18 and 65 years of age were recruited for consultation at the Fournier Institute with a view to participating in this randomised, double-blind study.

Women who had had at least three episodes of LUI over the preceding 6 months and who had intercourse on more than one occasion every fortnight could be included in the study. After having given their written, informed consent, the patients were divided into three groups according to the randomisation table. For 45 days following their inclusion in the study, the patients had to take one capsule of either GynDelta® (group A), an extract of *Vaccinium macrocarpon* containing 36 mg of pro-anthocyanidin A (group B) or a placebo (group C) within 6 hours of sexual intercourse. The patients were reviewed after 45 days. The number of recurring episodes of cystitis, the length of time to onset of the first bout of cystitis after inclusion and product tolerability were evaluated. The evaluation was made on the basis of the patients' interview and the study of a calendar completed by the patient and listing the following information: details of sexual relations during this period, administration of the allotted treatment, any recurrence of cystitis, the possible consumption of antibiotics and side effects.

Statistical analysis

The case report forms and follow-up sheets were the subject of dual interactive input using Clintrial 4.4 software. The transfer and quality control were carried out using SAS software version 8.2.

Analysis of the length of time to onset of recurrence was carried out using the Kaplan Meyer method. The number of relapse patients was analysed according to the method of Holm, Hochberg, and Benjamini and Hochberg.

Results

Overall, out of the 120 patients entered into the trial, dossiers for 116 patients proved eligible for analysis: 38 in group A (GynDelta®), 39 in group B (36 mg of PAC) and 39 in the placebo group.

An average of 8 cases of cystitis per year

The average age of the patients was 35.7 years (group A: 37 years, group B: 33.1 years and group C: 36.9 years). Out of the 116 dossiers eligible for analysis, none of the women was pregnant, 6 were pre-menopausal (5.3%*)* and 17 were menopausal (14.9%*)*.

The average annual number of cases of cystitis in the patients' medical history was 8 episodes per year (group A: 8.1, group B: 8.4, group C: 7.4).

Table 1 shows the symptoms most frequently reported by patients during episodes of cystitis. There were over 100 symptoms since the patients described several related symptoms.

Thirteen patients (11.2%*)* presented with cystitis on the day of inclusion. Eleven received a single dose of fosfomycine trometamol and two were treated with oral norfloxacine for 4 or 8 days.

Four times fewer recurring episodes with GynDelta®

Out of the 120 patients included in the study, 9 were lost to follow up including 4 dossiers, which were rejected as they were incomplete in terms of patient description. 111 women took the treatment allocated to them and could, therefore, be analysed.

Table 1 – Cardinal symptoms

	Number	Percentage
Female patients	116	
Patients presenting with at least one cardinal symptom	115	99.1
Pollakiuria	109	94.0
Burning sensation on micturition	114	98.3
Turbid urine	74	63.8
Malodorous urine	53	45.7
Sub-pelvic pain	43	37.1
Pruritus	18	15.5

Table 2 - Recurrent episodes of cystitis associated with sexual intercourse during the study

	GynDelta®	Group B	Placebo	Total
Number of female patients	37	37	37	111
Cystitis due to sexual relations n (%)				
No	33 (89.3)	30 (81.1)	21 (56.8)	84 (75.7)
Yes	4 (10.8)	7 (18.9)	16 (43.2)	27 (24.3)

Tolerance

Eleven female patients out of 116 (9.5%) reported an undesirable side effect during the study: 3 in the GynDelta® group (headaches, gastralgia), 8 in group B (gastralgia, nausea) and none in the placebo group. None of these side effects triggered premature treatment withdrawal. It should be noted that, two patients, one in the GynDelta® group and the other in the B group, developed a vaginal infection during treatment.

Table 2 shows the distribution of women who developed one or more episodes of cystitis triggered by sexual relations during the follow-up period.

Overall, almost one in 4 patients (24.3%) experienced a recurring episode of cystitis during the study with considerable variations depending on the treatment received. Women in the GynDelta® group, for instance, had four times fewer relapses than those in the placebo group (p = 0.005) and almost two times fewer relapses than those receiving 36 mg of PAC (group B) [diagram 1].

If the recurrence levels are statistically compared within the 3 treatment groups, a significant difference is evident in favour of GynDelta® treatment, regardless of the statistical method used (Table 3).

Diagram 2 shows the length of time to onset of recurring cystitis during tre

The longest period to the reappearance of the first episode was recorded i B and 4 days for the placebo group). The results are independent of the leng on average, in each group) and the average number of sexual relations bet the GynDelta® group; 8.4 in the B group; 11.5 in the placebo group).

The patient's clinical evaluation of the 3 treatments is listed in Table 4.

The product was assessed as good or very good by 88.9% of patients in the GynDelta® group compared with 80.6% in group B and 52.9% in the placebo group.

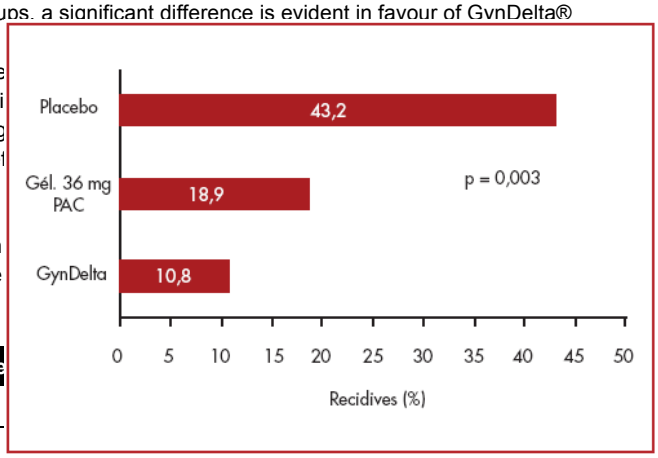

Schéma 1 - Pourcentage de femmes ayant une récidive de cystite au cours de l'étude.

Table 3 - Statistical evaluation of the results according to treatme

Statistical tests	p-value			
	Chi^2	Holm method		
GynDelta® versus placebo	0.002	0.005	0.005	0.005
Group B versus placebo	0.024	0.048	0.048	0.036

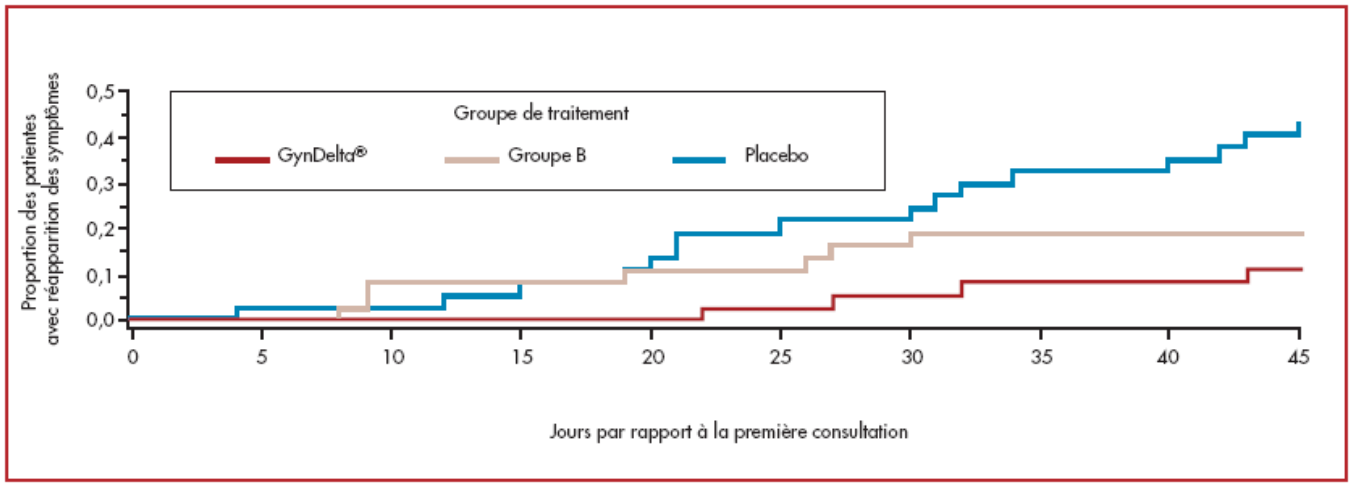

Schéma 2 - Délai de survenue de la réapparition des symptômes. Courbe de survie (méthode de Kaplan-Meier). Les réapparitions des symptomes répertoriés dans les fiches de suivi des trois patientes (004 et 025 du groupe B, 015 du groupe GynDelta®) ne sont pas prises en considération dans ce graphique. En effet, l'investigateur n'a pas reconnu ces symptômes comme étant des cystites.

No. of days with reference to the first consultation

Diagram 2 - Length of time to onset of the reappearance of symptoms. Survival curve (Kaplan-Meier method). The reappearance of the symptoms listed in the follow-up files of the three patients (004 and 025 in group B, 015 in the GynDelta® group) is not taken into account in this graph. In fact, the Investigator did not recognise these symptoms as being those of cystitis.

Table 4 - Patient's global assessment of treatment on completion of treatment

	GynDelta®	Group B	Placebo	Total
Number of female patients	36	36	34	106
Global treatment assessment n (%)				
Very good	29 (80.6)	18 (50.0)	18 (52.9)	65 (61.3)
Good	3 (8.3)	11 (30.6)	0 (0.0)	14 (13.2)
Moderate	2 (5.6)	2 (5.6)	7 (20.6)	11 (10.4)
Nil	2 (5.6)	5 (13.9)	9 (26.5)	16 (15.1)
Aggravation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Discussion

There is a high average number of cases of cystitis in the patients' medical history. This can be attributed to the fact that consultations at the Fournier Institute specialise in the management of recurrent uro-genital infections and treat patient who often experience numerous recurring episodes.

The symptoms most often listed by the patients are, unsurprisingly, pollakiuria and burning sensation on micturition.

The results obtained with GynDelta® highlight efficacy in the prevention of recurrent cystitis, both in the number of patients with recurring episodes of cystitis and in the length of time to onset of the first bout of recurrence. GynDelta® is clinically more effective than the capsules containing 36 mg of PAC as regards the number of patients experiencing a relapse, with a greater level of statistical significance compared with the placebo, even if the patients' global evaluation is comparable.

A non-negligible placebo effect can be observed with over 56% of patients not experiencing a relapse in this group. This result is certainly consistent with the duration of the study (45 days). A longer study period would, most certainly, have yielded less favourable results for the placebo group.

Side effects were seldom observed during the study and were of moderate intensity as they did not result in any study drop-outs.
Overall, the prevention of recurrent cystitis is a basic step for ensuring a patient's quality of life. Although long-term antibiotic treatment has proved effective up to a point, the impact of such treatments on the patients themselves and on the risk of developing mid-term resistance should be emphasised. Extracts of *Vaccinium macro-carpon* are considered as an effective alternative to long-term antibiotics by preventing the deleterious effects of the latter. The study conducted at the Fournier Institute prove that administration of a single GynDelta® capsule within 6 hours following intercourse has a genuine, protective effect as regards recurring bouts of cystitis. It also shows that the concentration of 36 mg pro-anthocyanidins A, sometimes considered as the lower limit of efficacy, must be reconsidered or that other substances contained in GynDelta® play an active role in preventing the recurrence of cystitis via antibacterial and/or anti-inflammatory action.

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