Original Articles

Clinical trial comparing the activity and efficacy of Ibuprofen isobutanolammonium vs Benzydamine hydrochloride, applied as vaginal irrigations, in patients with vaginitis

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Summary

This study was conducted on 30 female patients (average age: 40.5 ± 11 years, age range 19-65), affected by vulval and/or vaginal phlogosis with a prevalence of uterine fibromyomatosis and metrorrhagia of a varied nature. Sixteen patients were affected with vulvitis and 14 with vulvovaginitis. Fifteen patients were assigned to the treatment with Ibuprofen isobutanolammonium and 15 to the treatment with Benzydamine hydrochloride. Both the subjective symptoms (burning and itching) and the objective symptoms (erythema, oedema, exudation) showed a marked reduction as early as the third day of treatment and the comparison between the score at the start of treatment and on day three of the treatment was highly significant in both study groups ($p < 0.01$). This improvement was, however, more marked in the group of patients treated with ibuprofen isobutanolammonium, where a more rapid reduction of both the subjective and objective symptoms was observed on the third day. This trend, although not as marked as on the third day, was confirmed at the end of the study, on the seventh day.

Key words: Ibuprofen isobutanolammonium; Benzydamine hydrochloride; Vaginal irrigation; Vaginitis.

Introduction

The most common forms of vaginal infection are bacterial infections (30-35%), followed by mycotic infections (20-25%), and those caused by Trichomonas vaginalis (10%). Mixed pathologies, that is, vulvovaginitis caused by two or more pathogens, are observed in 15% of the cases [1]. Vaginal infections develop when high concentrations of anaerobic organisms, Gardnerella Vaginalis and Mycoplasma, prevail by a competitive mechanism over the lactobacilli normally present in the vaginal ecosystem [2, 3].

Numerous factors contribute towards the development of vaginal infections [4]. Patients with vaginal infections present different signs and symptoms [2, 5] which, although non-specific, jointly contribute towards a diagnosis of vaginal infection [2, 3, 4].

The treatment of all forms of vulvovaginal infection, even when carried out with appropriate antibiotic preparations, is very often complicated by a high percentage of relapses related to: 1) the selection of bacterial strains resistant to the antibiotics normally used; 2) the necessarily limited duration of the treatment; 3) persistence of the micro-environmental conditions which promote the infection.

In vitro studies with Ibuprofen, a non-steroidal anti-inflammatory drug widely used due to its analgesic, anti-pyretic and anti-inflammatory properties, have demonstrated that it possesses a moderate anti-microbial activity against various types of bacteria and Candida Albicans [6, 7]. Data have recently been reported on the antibacterial and anti-fungal activity of Ibuprofen isobutanolammonium against Gram-positive bacteria (Staphylococcus aureus, Streptococcus faecalis), Gram-negative bacteria (Pseudomonas aeruginosa, Escherichia Coli, Gardnerella vaginalis) and Candida Albicans [8]. Ibuprofen isobutanolammonium consequently possesses singular characteristics: a powerful anti-inflammatory action together with a significant bactericidal action [9].

Its antibacterial activity is exerted on Gram-positive bacteria, as well as on many gram negative bacteria, especially when the pH tends to be alkaline [10].

The purpose of this study was to ascertain the therapeutic activity and tolerability of "1-hydroxymethyl-1-methyl-ethyl ammonium" of Ibuprofen, gynaecological solution, in a controlled study versus Benzydamine hydrochloride, in patients with vulval and/or vaginal phlogosis.

Materials and methods

The clinical trial was conducted on 30 female patients, affected by vulval and/or vaginal phlogosis, attending our out-patient department during routine clinical practice.

Criteria for exclusion from the study were: pregnant patients; the use of medicinal preparations liable to interfere with the study drugs.

The patients were treated, according to a pre-established sequence, with Ibuprofen isobutanolammonium or with Benzydamine hydrochloride for seven consecutive days. The dosage for both groups of patients was two applications of the drug per day, both as an external wash in the case of vulval phlogosis and as an intra-vaginal application by means of a special applicator.

The study drug efficacy parameters, measured before commencement of the treatment, after three and seven days (end of the clinical trial) were the subjective clinical symptoms:

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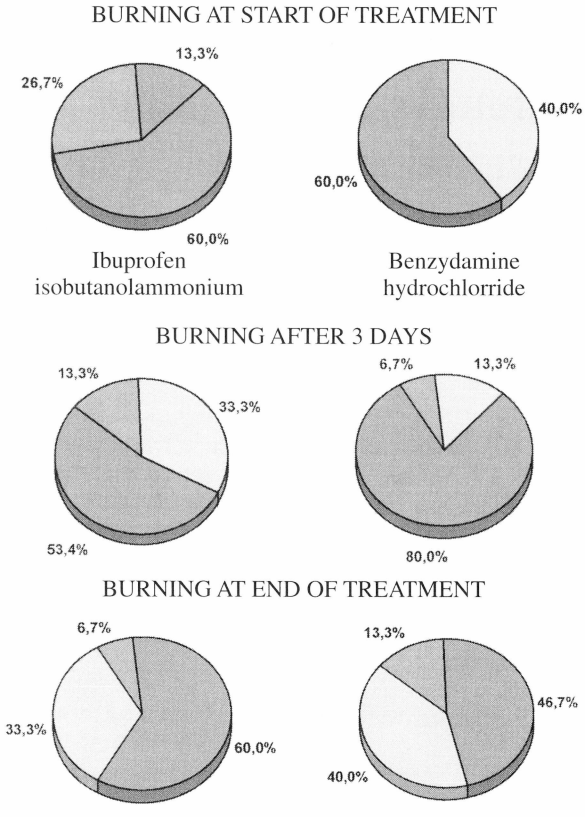

Figure 1. — Trend of intensity of the subjective burning symptom in the two groups of patients before treatment, on the 3rd and 7th day.

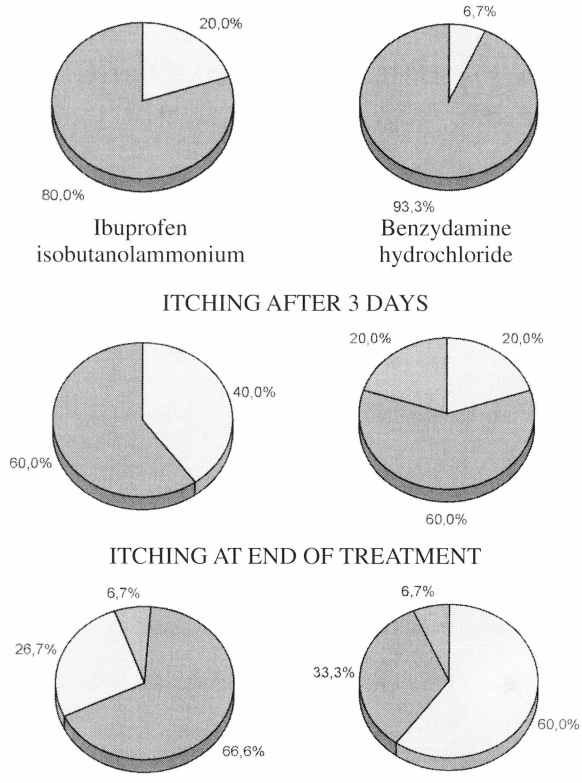

Figure 2. — Trend of intensity of the subjective itching symptom in the two groups of patients before treatment, on the 3rd and 7th day.

burning and itching; and objective clinical signs: erythema, oedema and exudation. Evaluation of the signs and symptoms was carried out by means of a scale of points ranging from 0 to 3 and then adding up the points within each category of parameters (subjective and objective).

Tolerability was monitored by evaluating the following laboratory parameters before commencement and at the end of the treatment: glycaemia, azotemia, SGOT, SGPT, alkaline phosphatase, bilirubin, proteinemia, haematocrit, haemoglobin, leukocytes and erythrocytes. At the end of the clinical trial, a clinical opinion was expressed on the therapeutic efficacy of the study drugs, obtained according to the following scale: excellent, good, mediocre, null.

The efficacy of the treatment within each group was evaluated by the Wilcoxon test for paired data between the score at check-up and the baseline score. The two groups were statistically compared by the Mann-Whitney test on the differences of the scores on the third day and at the end of the clinical trial (seventh day) compared to the baseline score. The means of the laboratory values, within each group, were statistically evaluated by the T-test for paired data at the start and end of the treatment. In order to obtain a qualitative clinical evaluation, the confidence intervals of the means were calculated.

Results

The average age of the patients recruited into the study was 40.5 ± 11 years (age range 19 to 65).

The principal pathology was of a gynaecological nature with a prevalence of uterine fibromyomatosis and metrorrhagia of various kinds. Sixteen patients were affected with vulvitis and 14 with vulvovaginitis (Table 1).

Fifteen patients were assigned to the treatment with Ibuprofen isobutanolammonium and 15 to the treatment with Benzydamine hydrochloride.

Before commencement of the treatment, the subjective symptoms (burning and itching) and objective symptoms (erythema, oedema, exudation) were comparable in the two groups of patients (Tables 2, 3).

Both the subjective symptoms (Figures 1 and 2) and the objective symptoms (Figures 3, 4 and 5) showed a

Table 1. — *Distribution of the pathologies in the two treatment groups.*

	Ibuprofen isobutanolammonium	Benzydamine hydrochloride
Vulvitis	7	9
Vulvovaginitis	8	6

Table 2. — *Overall trend of the subjective clinical symptoms (itching and burning) in the two treatment groups: mean ± standard deviation.*

	Ibuprofen isobutanolammonium	Benzydamine hydrochloride
Baseline	4.93 ± 0.88	5.53 ± 0.64
After 3rd day	1.40 ± 0.91	3.93 ± 0.80
End of Treatment	0.87 ± 1.19	1.43 ± 1.24

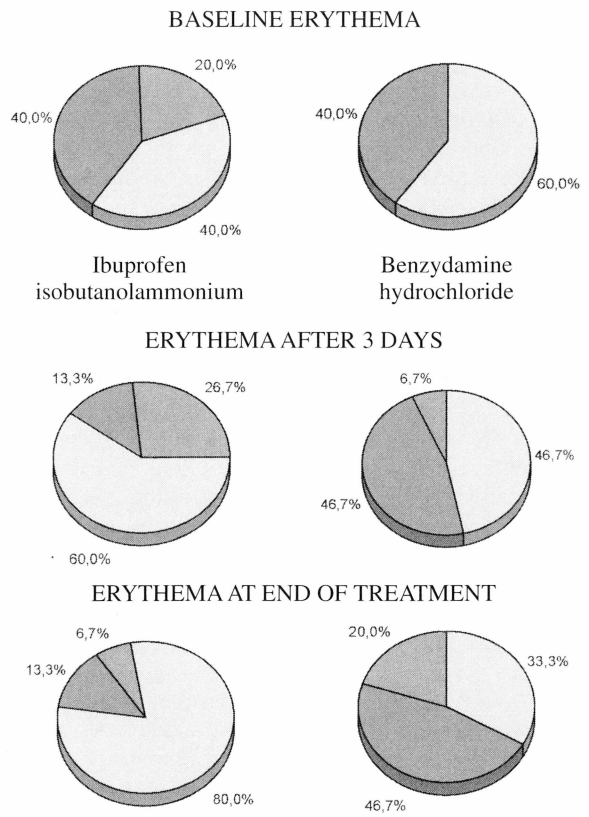

Figure 3. — Trend of intensity of the objective erythema symptom in the two groups of patients before treatment, on the 3rd and 7th day.

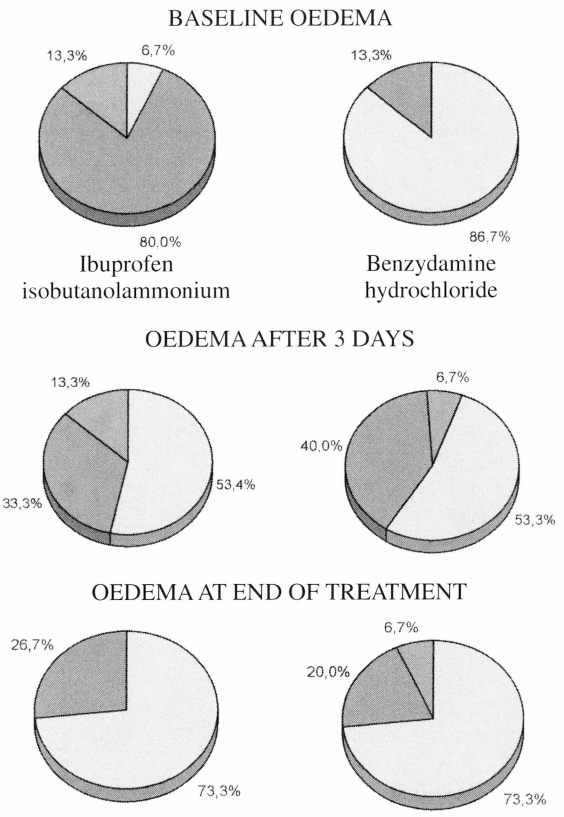

Figure 4. — Trend of intensity of the objective oedema symptom in the two groups of patients before treatment, on the 3rd and 7th day.

marked decrease as early as the third day of treatment and the comparison between the scores at the beginning of the therapy and on the third day of treatment was highly significant in both study groups ($p < 0.01$).

The reduction in the scores for both categories of subjective and objective symptoms, however, was more marked in the group of patients treated with Ibuprofen isobutanolammonium. In fact, at this evaluation time, the percentages of patients treated with Ibuprofen isobutanolammonium with no/slight subjective burning and itching symptoms were 86% and 100%, respectively. While the percentages of patients treated with Benzydamine hydrochloride, who showed no/slight values for the same symptoms were 13% and 20%, respectively. The same trend was observed for the subjective symptoms (Table 4). This result was confirmed by the comparison between the paired data relating to the third day of treatment in the two groups which proved to be highly significant in favour of Ibuprofen isobutanolammonium ($p < 0.01$). At the end of the treatment (7th day), even though a further reduction in the signs and symptoms was observed, the differences between the two study groups were not statistically significant (Tables 2 and 3).

The trend of the scores relating to the clinical opinion on the therapeutic efficacy of the study drug is graphically illustrated in Figures 9 and 10.

The means of the blood chemistry test values did not exhibit any statistically significant differences at the end of the study compared to the mean values at the start of treatment either in the group of patients treated with Ibuprofen isobutanolammonium or in the group of patients treated with Benzydamine hydrochloride. In addition, the confidence intervals of the means fully coincided between the start and end of treatment and fell within the normal ranges of values indicated for the two treatment groups (Table 5; Figures 6, 7, 8).

Table 3. — *Overall trend of the objective clinical symptoms (erythema, oedema, exudation) in the two treatment groups: mean ± standard deviation.*

	Ibuprofen isobutanolammonium	Benzydamine hydrochloride
Baseline	5.67 ± 0.82	6.13 ± 0.83
After 3rd day	2.00 ± 1.46	3.87 ± 1.19
End of treatment	0.80 ± 1.08	1.33 ± 1.11

Table 4. — *Percentage of patients of each treatment group with no/slight subjective and objective symptoms on the third day of treatment.*

No/Slight Symptoms	Ibuprofen isobutanolammonium	Benzydamine hydrochloride
Burning	86%	13%
Itching	100%	20%
Erythema	86.7%	46.7%
Oedema	86.7%	58%
Exudation	93.3%	86.7%

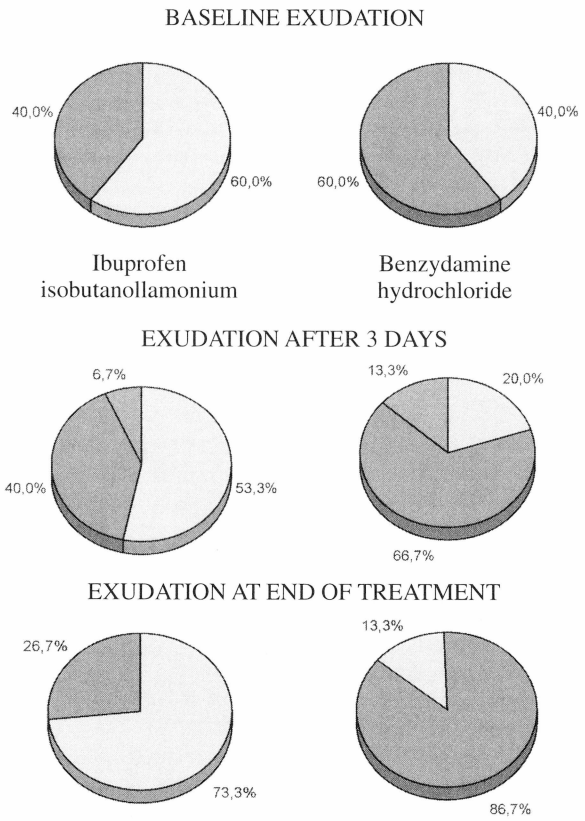

Figure 5. — Trend of intensity of the objective exudation symptom in the two groups of patients before treatment, on the 3rd and 7th day.

One very interesting datum was the one relating to local and general tolerability, which was found excellent in both treatment groups (Table 5).

In both treatment groups, compliance with the treatment was excellent, considering that no side-effects were observed.

Conclusions

In relation to the exceptional increase in the spread of vaginitis sustained by various pathogens and in the presence of inconclusive data on sexually transmitted diseases, we conducted a clinical trial to evaluate the activity of a drug endowed with a marked anti-phlogistic and analgesic activity.

The vagina can be considered as an organ in which different bacterial species, and in particular lactobacilli, interfere with the host, thereby giving rise to a state of dynamic equilibrium, responsible for alterations of vaginal pH [11].

It is well known fact that, to develop, lactobacilli need glycogen, whose presence is assured by the epithelial lining of the vaginal and exocervical mucous membrane, in particular in their outermost layers. Lactic acid, which is responsible for the acidity of the environment, derives from the scission of the glycogen accumulated in it.

A further level of interaction intervenes when exogenous micro-organisms are introduced into the vaginal environment, which gives rise to competition between exogenous micro-organisms and endogenous bacterial flora [12].

The therapeutic strategy must consequently be oriented along two different lines which, on the one hand, tend to normalise the altered vaginal environment and, on the other, to eliminate the pathogenic bacterial flora.

These take the form not only of surgical operations to remove macroscopic anatomical alterations, but also of pharmacological type treatments aimed at curing a state of hypo-estrogenism (estrogens) or a condition of phlogistic pathology (cortisones and anti-inflammatory drugs), as well as selective interventions (antibiotics and chemotherapy) and non selective interventions (disinfectants and vaginal irrigations) capable of eliminating the species responsible for the pathological symptoms.

As far as prevention is concerned, it is important to underline the validity of old remedies such as: a) accurate

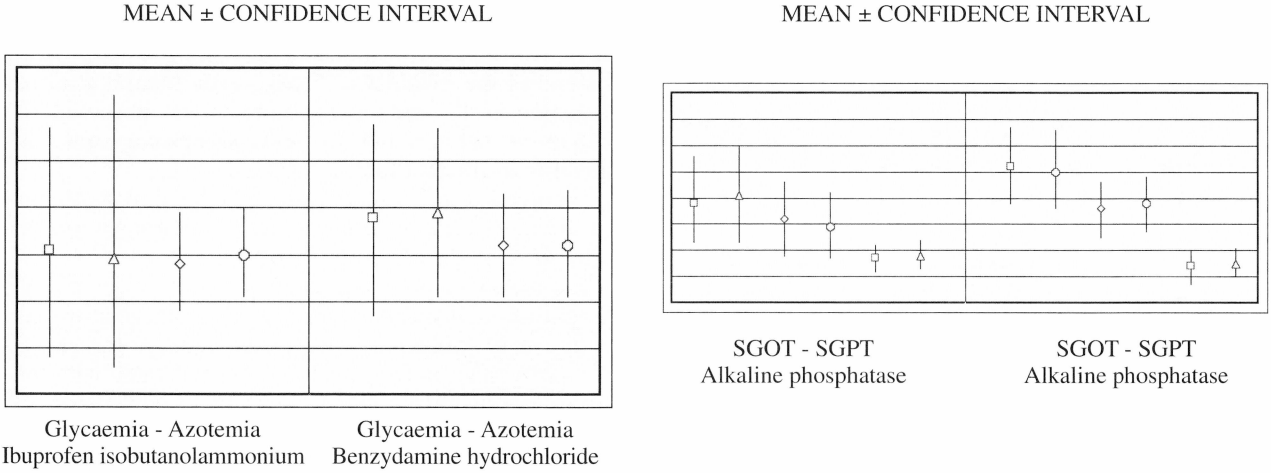

Figure 6. — Glycaemia, azotemia, SGOT, SGPT and alkaline phosphatase laboratory parameter values before treatment and on the 7th day in the two study groups: mean ± confidence interval.

Table 5. — *Blood chemistry tests of the two groups of patients before the start and at the end of treatment (7th day: mean values ± confidence interval of the mean).*

		Ibuprofen isobutanolammonium			Benzydamine hydrochloride		
	u.m.	- 95%	Mean	+ 95%	- 95%	Mean	+95%
Baseline glycaemia		92.8	102.6	112.4	97.1	105.2	113.2
End of treatment glycaemica		92.1	101.8	115.6	98.5	105.7	112.9
Baseline azotemia		27.5	31.5	35.5	28.6	32.9	37.2
End of treatment azotemia		28.2	32.1	36.1	28.5	32.9	37.4
Baseline SGOT		20.5	23.7	27.0	23.6	26.5	29.3
End of treatment SGOT		20.5	24.2	27.9	23.1	26.1	29.1
Baseline SGPT		19.6	22.3	25.0	20.8	23.1	25.3
End of treatment SGPT		19.4	21.9	24.3	21.5	23.5	25.5
Baseline Alk. phosphatase		8.3	9.3	10.4	7.4	8.7	10.0
End of treatment Alk. phosphatase		8.4	9.6	10.8	8.0	9.0	10.1
Baseline bilirubinaemia		0.72	0.79	0.87	0.68	0.76	0.83
End of treatment bilirubinaemia		0.72	0.77	0.83	0.69	0.73	0.77
Baseline proteinemia		6.5	6.7	6.9	6.5	6.7	6.8
End of treatment proteinemia		6.6	6.8	7.0	6.5	6.7	6.8
Baseline haematocrit		42.1	43.9	45.7	42.8	44.0	45.2
End of treatment haematocrit		42.1	43.7	45.4	42.2	43.5	44.7
Baseline haemoglobin		13.7	14.0	14.3	13.6	13.9	14.2
End of treatment haemoglobin		13.7	14.0	14.2	13.6	13.9	14.2
Baseline leukocytes		8.1	8.4	8.6	7.9	8.2	8.4
End of treatment leukocytes		8.2	8.4	8.6	8.0	8.2	8.5
Baseline erythrocytes		5.0	5.1	5.2	4.9	5.0	5.1
End of treatment erythrocytes		5.0	5.1	5.2	4.9	5.0	5.1

hygiene of the external genitals with soap, especially acid soaps and water, b) correct and careful use of vaginal irrigations.

The latter remedy is undoubtedly effective in that it affords gentle and constant endovaginal cleansing, respecting the normal bacterial flora and maintaining the vaginal pH in normal physiological conditions.

Bearing in mind these premises, the data obtained from this clinical trial indicate that the association of Ibuprofen and Isobutanolammonium may be extremely useful in situations of vaginal dysmicrobism.

The possible mechanisms whereby ammonium derivatives exert their activity are the following: a) on the bacterial proteins: by denaturing the structural proteins and destroying the enzymes, b) on the permeability of the bacterial cell, c) on the bacterial metabolism: at low concentrations they induce inhibition of aerobe and anaerobe respiration and inhibition of lactic acid oxidation, stimu-

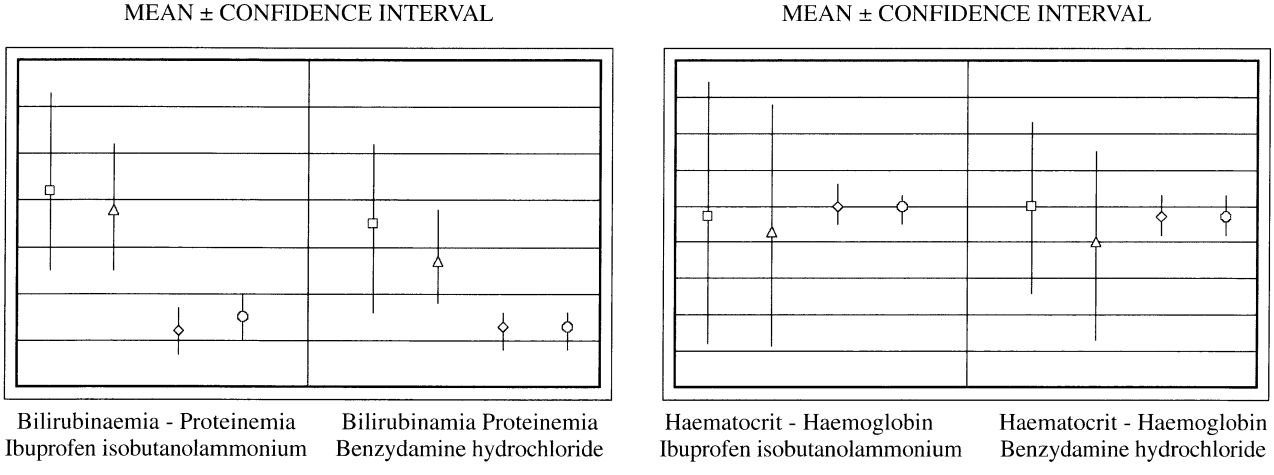

Figure 7. — Bilirubinaemia, proteinemia, haematocrit and haemoglobin laboratory parameter values before treatment and on the 7th day in the two study groups: mean ± confidence interval.

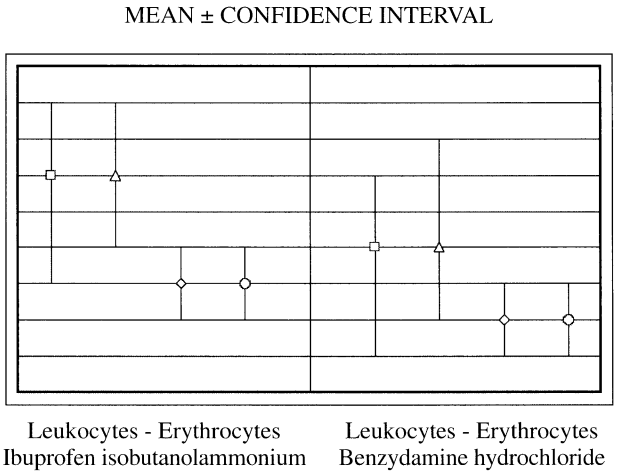

Figure 8. — Leukocyte and erythrocyte laboratory parameter values before treatment and on the 7th day in the two study groups: mean ± confidence interval.

lation of glycolysis with an increase in lactic acid, d) on the adhesion of the bacteria to the epithelial cells [8].

This consideration accounts for the antibacterial and anti-inflammatory activity of Ibuprofen isobutanolammonium.

Precisely because of this particular association, we believe that there may be a strengthening of its efficacy in vaginal inflammatory pathologies, as indicated by the data of this clinical trial.

It is important to underline that all the patients recruited in the study showed a decided improvement in the subjective and objective parameters as of the third day of treatment with both pharmaceutical preparations. This improvement was found to be more marked in the group of patients treated with Ibuprofen isobutanolammonium, where in fact, a more rapid reduction in both the subjective and objective symptoms was observed on the third day.

This trend, even though not as markedly as on the third day, was confirmed at the end of the study, on the seventh day.

Consequently, it is possible to observe that, on the whole, the group of patients treated with Ibuprofen isobutanolammonium showed a distinct improvement as regards the more irritating subjective and objective symptoms.

In conclusion, in association with a correct culture of endovaginal preventive hygiene with pharmacological preparations, we believe that the use of therapeutic preparations such as Ibuprofen isobutanolammonium can be extremely useful in preventing recurring vaginal pathologies such as vaginitis and vaginosis.

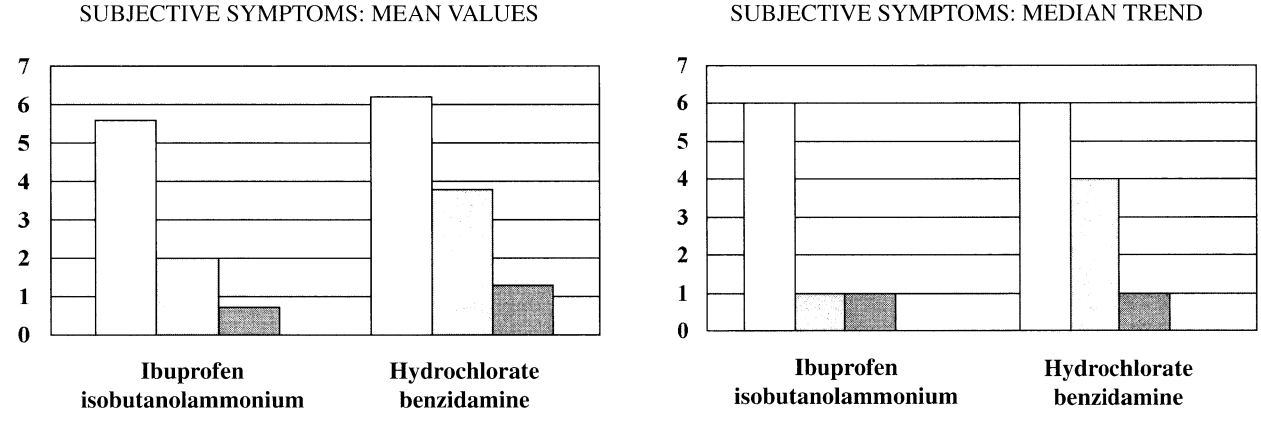

Figure 9 — Trend of subjective symptoms in the two treatment groups: mean values and median trend.

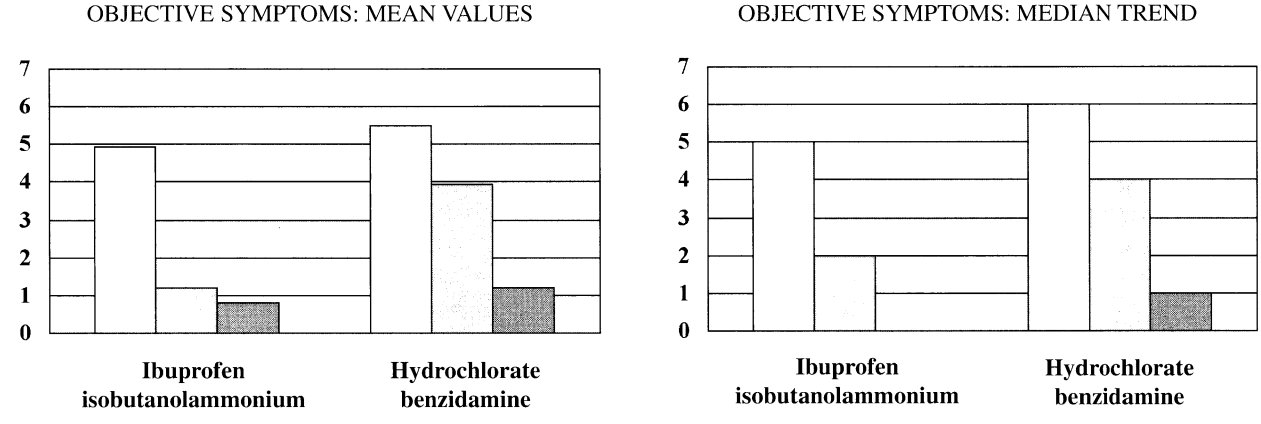

Figure 10. — Trend of the objective symptoms in the two treatment groups: mean values and median trend.

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