USE OF TOPICAL BENZYDAMINE IN GYNECOLOGY

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SUMMARY

To evaluate the topical anti-inflammatory activity of benzydamine when used as 0.1% solution for vaginal douche, a double blind, parallel group, randomized clinical trial was carried out on 30 patients with vaginitis following internal radiotherapy for carcinoma of the uterus. The patients were divided into 3 groups, one being treated with 0.1% benzydamine plus tricetol as preservative, one with 0.1% benzydamine alone, and one with placebo. Treatment began 12-24 hours after radiotherapy. Benzydamine was found to be significantly superior to placebo in its overall topical anti-inflammatory activity both after 5 and 15 days of treatment. Tricetol did not interfere with the therapeutic effect of benzydamine.

INTRODUCTION

Benzydamine's anti-inflammatory properties have already been well documented in different fields of medicine ([1-13]).

This compound belongs to the group of anti-inflammatory agents which act directly on inflammation by stabilizing cell and lyposomal membranes and by inhibiting the synthesis of some prostaglandins ([14-16]).

Benzydamine is used both topically and systematically (by the oral, parenteral and rectal routes); as far as its topical uses are concerned it is interesting to note that it is well absorbed through the skin, reaching higher concentrations in the underlying inflamed tissue than after oral administration ([17-20]).

In addition to its anti-inflammatory activity benzydamine has been shown to have analgesic, local anaesthetic and antimicrobial effects ([21-24]).

On the basis of the above considerations, we decided to investigate topical benzydamine in gynaecological practice, dividing our study into two parts. The first part consists of a controlled clinical trial on vaginitis following topical radiotherapy and is aimed at demonstrating the anti-inflammatory activity of 0.1% benzydamine vaginal douche. The second part, consisting of 2 uncontrolled clinical trials on non-specific bacterial vaginitis and post-radiotherapy vaginitis, was carried out in order to provide supporting evidence of its anti-inflammatory activity as well as some information on its range of therapeutic action and on the response of individual symptoms and signs to treatment.

MATERIAL AND METHODS

Controlled clinical trial on post-radiotherapy vaginitis

A double blind, randomized clinical trial was carried out on 30 patients aged 30 to 77 years with vaginitis following internal radiotherapy for carcinoma of the cervix or body of the uterus.

Table 1. — *Controlled study on post-radiotherapy vaginitis.*

Product	Age in years	Mean total score before treatment
Benzydamine plus preservative	48-77 (mean: 63.5)	5.4
Benzydamine alone	30-70 (mean: 55.6)	5.4
Placebo	45-76 (mean: 59.1)	5.0

Table 2. — *Controlled study on post-radiotherapy vaginitis. Distribution of patients in the 3 experimental groups according to the site, type and stage of cancer.*

Site	Type and stage of cancer	Treatment		
		Benzydamine plus preservative	Benzydamine	Placebo
Body of the uterus	Adenocarcinoma			
	Stage I	3	6	3
	Stage II	1	0	1
Portio vaginalis	Epithelioma			
	Stage I	1	1	2
	Stage II	2	2	2
	Stage III	3	1	0
	Epithelioma or Adenocarminoma Undetermined stage	0	0	2

They were divided into 3 groups of 10 each, one being treated with 0.1% benzydamine vaginal douche(*), one with 0.1% benzydamine alone(**) and one with placebo(***). The groups were similar with respect to age and the initial severity of vaginitis (table 1) and also with respect to the type and site of cancer (table 2) and the dose of radiation received (table 3).

(*) 1 ampoule of Tantum Rosa® (liquid) concentrate containing 0.5 g of benzydamine plus tricetol as preservative, diluted in 500 ml of water.

(**) 1 ampoule of liquid concentrate containing 0.5 g of benzydamine hydrochloride in distilled water, diluted as above.

(***) Vehicle of 1 ampoule of Tantum Rosa® without the preservative tricetol, diluted as above.

As far as adenocarcinoma of the body of the uterus was concerned, abdominal hysterectomy and bilateral salpingo-oophorectomy was performed in all patients prior to radiotherapy so that irradiation of the vaginal vault was used only prophylactically and was limited to 27 m.c.d. (millicurie destroyed). With regard to the vaginal portio of the cervix, radiotherapy was used either alone or pre- or post-operatively (doses ranged from 36-72 m.c.d.).

Douching with the products under study was carried out twice daily for 15 days, treatment being begun 12-24 hours after radiotherapy.

The severity of symptoms and signs was rated on a 3 point scale (0 = absent, 1 = moderate, 2 = severe) on admission to the trial and after 5 and 15 days of treatment, when the total scores were also recorded.

The following symptoms and signs were assessed:

pain
pruritus
tension
sensation of heat, dryness and burning
hyperemia (redness)
vaginal discharge
tenderness
oedema.

At the end of the 15 day treatment period the overall therapeutic effect, rated on the basis of the investigator's general

Table 3. — *Controlled study on post-radiotherapy vaginitis. Distribution of patients in the 3 experimental groups according to the dose of radiation received.*

Dose (m.c.d.)(*)	Benzydamine plus preservative	Benzydamine alone	Placebo
27	4	6	4
36	4	2	3
63	0	0	2
71	1	1	1
72	1	1	0

(*) m.c.d.: millicurie destroyed

clinical impression was graded as excellent, good, fair, slight and nil.

excellent = complete remission of symptoms and signs
good = marked improvement
fair = moderate improvement
slight = minimal improvement
nil = no improvement or worsening.

Both the rapidity and degree of improvement were taken into consideration in the evaluations.

Student's "paired t" test, the covariance analysis and the χ squared test were used for the statistical evaluation of the results.

Symptoms and signs were assessed as previously described on admission to the trial and at the end of the 5 day treatment period, when the overall therapeutic effect was also rated.

Cervico-vaginal cytology was used for confirming clinical findings in all patients.

b) *post-radiotherapy vaginitis*

An uncontrolled clinical trial was carried out on 30 patients aged 39 to 77 years (mean 61.5) with vaginitis following internal radiotherapy for carcinoma of the cervix or body of the uterus (vaginal portion of the cervix: 20, cervical canal: 3, body of the uterus: 7; stage I: 12, stage II: 8, stage III: 8). The radiotherapy had been associated with surgery in 13 cases.

0.1% benzydamine vaginal douche was used twice daily for 15 days, treatment being begun 12-24 hours after radiotherapy.

The severity of symptoms and signs on admission to the trial and after 5 and 15 days of treatment, and the investigator's general clinical impression at the end

Table 4. — *Controlled study on post-radiotherapy vaginitis. Comparison between the effects of benzydamine vaginal douche, benzydamine alone and placebo on the "mean total score" after 5 and 15 days of treatment.*

Product	Parameter	Before treatment	After treatment	
			5 days	15 days
Placebo	Mean ± SE	5.0 ± 0.7	3.1 ± 0.6	1.4 ± 0.4
No. of cases = 10	% change		−38.8	−72.0
Benzydamine alone	Mean ± SE	5.4 ± 0.5	2.0 ± 0.4	0.5 ± 0.2
No. of cases = 10	% change		−63.0	−90.7
Benzydamine plus preservative	Mean ± SE	5.4 ± 0.5	2.6 ± 0.6	0.7 ± 0.3
No. of cases = 10	% change		−51.9	−87.0

Covariance analysis	P	P
Placebo versus benzydamine	<0.01	<0.02
Placebo versus benzydamine plus preservative	<0.05	<0.01
Benzydamine alone versus benzydamine preservative	N.S.	N.S.

Uncontrolled clinical trials

a) *non-specific bacterial vaginitis*

An uncontrolled clinical trial was carried out on 50 patients aged 16 to 30 years (mean 25.1) with non-specific bacterial vaginitis of varying severity (17 severe, 21 moderate, 12 mild).

0.1% benzydamine vaginal douche (*) was used twice daily for 5 days.

(*) 1 ampoule of Tantum Rosa® diluted in 500 ml of water.

Table 5. — *Controlled study on post-radiotherapy vaginitis.*

Product	Therapeutic effect				Total No. of cases
	Excellent	Good	Slight	Nil	
Benzydamine plus preservative	0	8	2	0	10
Benzydamine alone	4	5	1	0	10
Placebo	0	4	5	1	10

of the 15 day treatment period were rated as previously described in the controlled section of the study.

A confirmatory vaginal smear was not taken in these patients since cytological findings could not be classified according to Papanicolau and since the inflammation was caused by radiation which could have destroyed any pre-existing bacteria, fungi or protozoa.

RESULTS

Controlled clinical trial on post-radiotherapy vaginitis

Table 4 compares the effects of the 3 douches on the mean total score after 5 and 15 days of treatment.

After 5 days of treatment a significant reduction in the total score occurred in all 3 groups (*). Nevertheless the mean percent decrease in the total score with placebo (38.8%) was lower than with either benzydamine plus preservative (51.9%) or benzydamine alone (63%), indicating the greater therapeutic effect of the medicated douches. The covariance analysis showed that there was no statistically significant difference between the effects of benzydamine plus preservative and benzydamine alone but both were significantly superior to placebo.

After 15 days of treatment a significant reduction in the total score again occurred in all 3 groups (*). As before, the mean percent in the total score with placebo (72%) was lower than with either benzydamine plus preservative (87%) or benzydamine alone (90.7%), indicating a greater therapeutic effect of the medicated douches. The covariance analysis showed that there was no statistically significant difference between the effects of benzydamine plus preservative and benzydamine alone but both were significantly superior to placebo.

At the end of the 15 day treatment period, excellent or good overall improvement occurred in 8 out of 10 patients treated with benzydamine plus preservative, in 9 treated with benzydamine alone and in 4 treated with placebo as shown in greater detail in table 5.

Uncontrolled clinical trials

a) *Non-specific bacterial vaginitis*

The severity of non-specific bacterial vaginitis before and after 5 days of treatment with benzydamine vaginal douche is shown graphically in figure 1.

The following overall therapeutic response was obtained at the end of the trial:

excellent: 29 cases (initially 4 severe, 13 moderate, 12 mild)
good: 7 cases (initially all 7 severe)
fair: 8 cases (initially all 8 moderate)
slight: 6 cases (initially all 6 severe).

With the 5 days of treatment, a definite improvement occurred in all patients in both symptoms (mainly pruritus vulvae, dyspareunia and at times pelvic pain) and the corresponding clinical signs (redness, leukorrhea and at times cervical erosion, either true or pseudo).

In particular, pruritus present in 13 cases disappeared in 7 and improved in 6; leukorrhea present in 44 cases, disappeared

(*) The significant reduction in the total score at each assessment time even with placebo may be explained by the fact that vaginitis following radiotherapy has a self-limiting course and moreover, like all other types of vaginitis, may also respond to some extent, to the purely physical action of any vaginal douche.

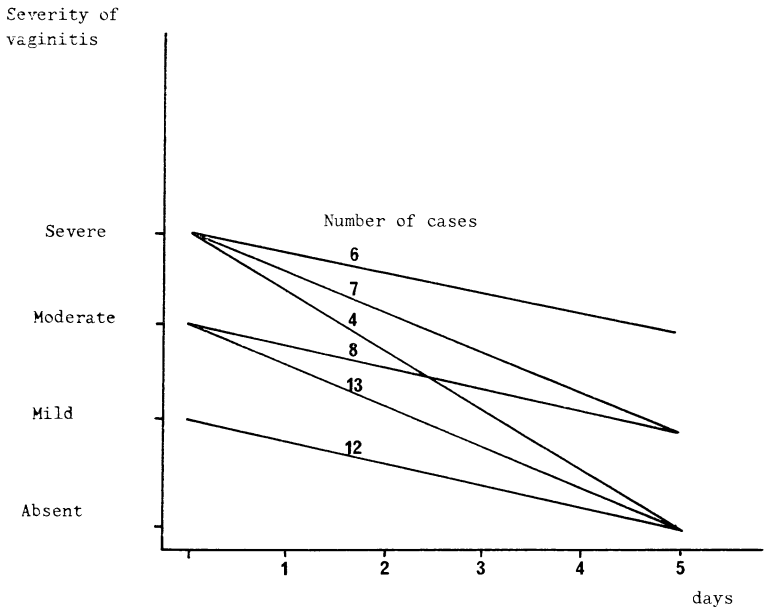

Fig. 1. — Uncontrolled study on non-specific bacterial vaginitis.

Table 6. — *Uncontrolled study on post-radiotherapy vaginitis. Effects of 0.1% benzydamine vaginal douche on the total score and on the scores for all symptoms and all signs after 5 and 15 days of treatment, in 30 patients with post-radiotherapy vaginitis.*

Parameter	Statistics	Before treatment	After treatment	
			5 days	15 days
Score for all symptoms	Mean	6.8	2.4	1.1
	± SE	0.40	0.27	0.20
	% change		−64.2	−83.3
	"t"		18.406 (***)	17.553 (***)
Score for all signs	Mean	3.1	0.9	0.4
	± SE	0.19	0.10	0.09
	% change		−69.6	−88.0
	"t"		14.262 (***)	16.155 (***)
Total score	Mean	9.9	3.4	1.5
	± SE	0.52	0.33	0.24
	% change		−65.9	−84.8
	"t"		22.065 (***)	20.934 (***)

(***) $P<0.001$

Table 7. — *Uncontrolled study on post-radiotherapy vaginitis. Effects of 0.1% benzydamine vaginal douche on the scores for individual symptoms after 5 and 15 days of treatment.*

Symptoms	No. of cases (a)	Statistics	Before treatment	After treatment	
				5 days	15 days
Burning	28	Mean	2.0	0.9	0.6
		± SE	0.10	0.07	0.11
		% change		−53.6	−69.6
		"t"		9.383 (***)	13.000 (***)
Tension	26	Mean	1.5	0.7	0.2
		± SE	0.11	0.11	0.08
		% change		−57.5	−87.5
		"t"		8.743 (***)	12.223 (***)
Heat	25	Mean	1.5	0.6	0.3
		± SE	0.16	0.13	0.9
		% change		−60.5	−81.6
		"t"		8.048 (***)	9.347 (***)
Pruritus	20	Mean	0.9	0.3	0.3
		± SE	0.11	0.10	0.10
		% change		−70.6	−70.6
		"t"		3.040 (**)	5.339 (***)
Pain	17	Mean	1.4	0.4	0.1
		± SE	0.15	0.12	0.06
		% change		−73.6	−95.7
		"t"		8.246 (***)	7.778 (***)

(a) No. of patients in whom the corresponding symptoms were present before treatment.
(**) $P<0.01$
(***) $P<0.001$

in 24 and improved in 20; redness present in 26 cases disappeared in 19 and improved in 7; dyspareunia present in 4 cases, was completely cured in 3 and remained unchanged in 1.

b) *Post-radiotherapy vaginitis*

Benzydamine vaginal douche produced a highly significant ($P<0.001$) average overall improvement (reduction of total score) and improvement in all symptoms and signs after both 5 and 15 days of treatment as shown in tables 6, 7 and 8.

After *5 days* of treatment the mean total score decreased by 65.9% the mean score for all symptoms by 64.2% and for all signs by 69.6%.

After *15 days* of treatment the mean total score decreased by 84.8%, the mean score for all symptoms by 83.3% and for all signs by 88%.

There was moreover, without exception, an improvement in each symptom and sign after both 5 and 15 days of treatment as shown in tables 7 and 8.

Overall improvement occurred in all the 30 patients treated at the end of the 15 day trial (excellent: 7, good: 19, fair: 4, slight or nil: 0).

SIDE EFFECTS

Side effects

No systemic side effects were observed in any of the 110 cases examined.

Only in patients with post-radiotherapy vaginitis did the dosage of benzydamine vaginal douche have to be halved in 12% of the cases, on account of the high irritability of the vaginal mucosa due to radiotherapy itself and to any underlying senile trophic changes.

both were significantly superior to placebo. The preservative tricetol did not consequently influence the therapeutic effect of benzydamine vaginal douche on post-radiotherapy vaginitis.

In the uncontrolled trial 0.1% benzydamine vaginal douche produced a significant improvement in each symptom and sign (burning, sensation of heat, tension, pruritus, pain, vaginal discharge, tenderness, oedema) after both 5 and 15 days of treatment.

Table 8. — *Uncontrolled study on post-radiotherapy vaginitis. Effects of 0.1% benzydamine vaginal douche on the scores for individual clinical signs after 5 and 15 days of treatment.*

Symptoms	No. of cases (a)	Statistics	Before treatment	After treatment	
				5 days	15 days
Vaginal discharge	30	Mean	2.2	0.8	0.4
		± SE	0.12	0.07	0.09
		% change		−62.1	−83.3
		"t"		13.462 (***)	15.503 (***)
Tenderness	26	Mean	1.2	0.2	0.0
		± SE	0.07	0.07	0.00
		% change		−86.7	−100.0
		"t"		18.028 (***)	15.990 (***)
Oedema	22	Mean	1.2	0.1	0.0
		± SE	0.09	0.07	0.00
		% change		−88.9	−100.0
		"t"		12.000 (***)	13.420 (***)

(a) No. of patients in whom the corresponding clinical signs were present before treatment.
(***) $P<0.001$

CONCLUSION

In post-radiotherapy vaginitis the pooled results of the 1 controlled and 1 uncontrolled clinical trial showed that 0.1% benzydamine vaginal douche produced overall improvement in 38 of the 40 patients treated i.e. 95% (excellent 7; good 27; fair 4; slight 2).

In the controlled study 0.1% benzydamine vaginal douche and the same concentration of benzydamine alone (douche without preservative) were found to be equivalent in their therapeutic effects but

Finally, 0.1% benzydamine vaginal douche had a good therapeutic effect on non-specific bacterial vaginitis, on the basis of the high overall improvement rate in each grading of severity.

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