SERUM LEVELS OF BENZYDAMINE FOLLOWING THE TOPICAL USE OF THIS DRUG IN GYNECOLOGY

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SUMMARY

The serum levels of benzydamine were studied after administration by vaginal douching (at a concentration of 0.1%) to patients with and without vaginal inflammation. In both experimental groups benzydamine produced similar serum concentrations which were lower than those obtained by other administration routes, excluding the possibility of eventual systemic effects. These data are a further confirmation that, whenever possible, topical use is preferable to systemic use in order to reduce the incidence of systemic side effects to a minimum and to obtain a more selective therapy.

Benzydamine is an anti-inflammatory drug with unique characteristics among which its selectivity of action in primary inflammatory forms (normoreactive) where the pathology remains localized, and the absence of some side effects [1, 2]. It is active by both the systemic [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13] and topical [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27] route. Since topical treatment has many advantages over the systemic one (i.e. better penetration through the skin and mucosa, better concentration in the inflamed tissue, disinfectant and locally anaesthetic properties, relatively low systemic absorption), it has gradually become the treatment of choice. The favourable results obtained by topical administration have ulteriorly increased benzydamine's possibilities of therapeutic use, also extending them to fields where other non-steroid anti-inflammatory agents do not find any use, such as inflammatory conditions of the oral cavity and gynecological disorders [1, 2].

Since the absorption of benzydamine under the form of cream, mouthwash and mouth-spray is already known [28, 29], it has been thought advisable to study its absorption also under the form of a vaginal douche. At the same time a correlation between the various types of administration used in therapy is provided, using the serum concentrations as a parameter of comparison.

MATERIAL AND METHODS

The study involved 12 in-patients with various gynecological disorders, 6 with and 6 without any vaginal inflammation on colposcopic and cytological examination.

Benzydamine was administered by single irrigation of 140 ml at a concentration of 0.1%, using a monodose container with a vaginal cannula.

At different times after administration a blood sample was withdrawn from the brachial vein of each patient, and the quantity of benzydamine present in the serum, obtained by centrifugation, was determined according to the following method.

Table 1.

No. Name	Age in years	Weight in kg	Diagnosis	μg/ml				
				1 h	2 h	4 h	8 h	24 h
1. N.D.	22	47	Abdominal and pelvic swelling	0.020	0.036	0.038	0.047	0.020
2. D.M.	29	54	Ovarian cyst	0.016	0.011	0.010	0.021	0.010
3. L.F.	42	60	Uterine fibromatosis	0.018	0.020	0.020	0.012	0.013
4. S.M.	28	56	Myoma of the uterine corpus	0.024	0.022	0.022	0.020	0.013
5. F.M.	24	68	Right tubal pregnancy	0.000	0.010	0.010	0.000	0.000
6. C.S.	43	62	Uterine fibroma	0.000	0.010	0.010	0.010	0.000
			Media ±	0.013	0.018	0.018	0.018	0.009
			ES	0.0042	0.0042	0.0045	0.0065	0.0032

Dilute 1 ml of serum with 0.1 ml of water, add 0.25 ml of sodium hydroxide 2N and extract for three times with 3 ml of heptane-n by stirring in Vortex for about 1 min and centrifugating each time for 5 min at 4000 r.p.m. Extract the organic phase with 1 ml of acetate buffer pH 4.8 I=0.1 by stirring for 1 min in Vortex and then centrifugating for 5 min at 4000 r.p.m. The buffer is put in microcuvettes and read at the fluorimeter Perkin Elmer Mod. 3000, using an excitation wave length of 303 nm and emission wave length of 360 nm (uncorrected values).

The quantity of benzydamine in the treated sample was calculated in base of known concentrations of benzydamine added to the control serum which was treated as described previously. With this method it is possible to detect concentrations of 0.010 μg/ml. The recovery of benzydamine added to blood is 66.6% ±3.81.

RESULTS

Table 1 reports the values of benzydamine's serum concentrations in gynecological patients with normal vagina and portio vaginalis on colposcopic and cytological examination.

Table 2.

No. Name	Age in years	Weight in kg	Colposcopy	Cytology	μg/ml				
					1 h	2 h	4 h	8 h	24 h
1. O.G.	55	50	Vaginitis	Trichomonas	0.020	0.022	0.010	0.010	0.000
2. S.I.	50	65	Epitheliased portio vaginalis with vaginitis	Monilia	0.015	0.010	0.022	0.020	0.013
3. C.C.	45	52	Vaginitis and numerous hypervascularised Nobothian cysts	Coryne-bacteria	0.020	0.030	0.010	0.011	0.010
4. B.M.	38	47	Vaginitis	Monilia	0.000	0.010	0.010	0.000	0.000
5. C.I.	44	62	Vaginitis, vascularised Nobothian cysts on anterior lip	Mixed flora	0.018	0.020	0.035	0.026	0.010
6. A.P.	45	72	Extensive ectopia with metaplasia, micropolyps of cervical canal, cervicitis with Nobothian cysts	Mixed flora	0.000	0.020	0.035	0.031	0.010
				Media ±	0.012	0.019	0.020	0.016	0.007
				ES	0.0039	0.0031	0.0050	0.0047	0.0023

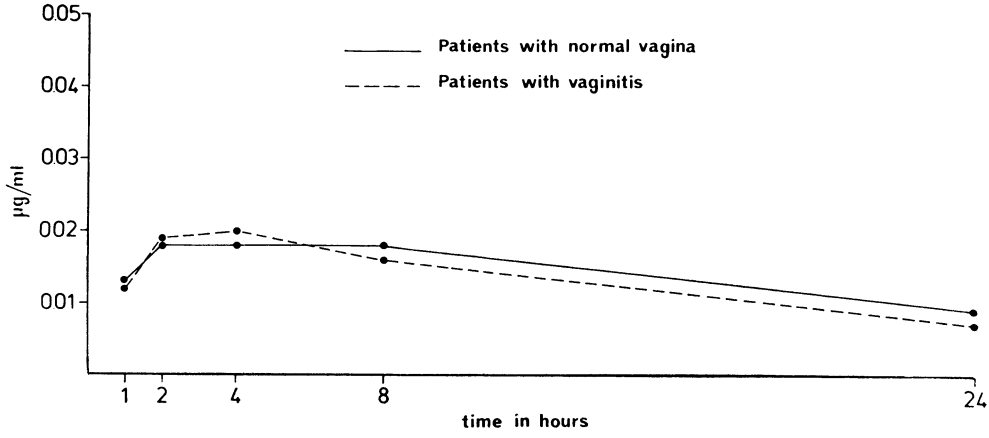

Fig. 1. — Comparison of time course of serum concentrations obtained in the two different groups of patients.

The results obtained indicate that benzydamine is present in the blood already 1 hour after administration (0.013 µg/ml), reaches a plateau (0.018 µg/ml) which remains constant from 2 to 8 hours, and is still present in the blood after 24 hours (0.009 µg/ml).

Table 2 reports the values of benzydamine's serum concentrations in patients with vaginal inflammation on colposcopic and cytological examination.

The results obtained indicate that benzydamine is present in the blood already 1 hour after administration (0.012 µg/ml), after 2 - 4 - 8 hours it reaches values of 0.019 - 0.020 - 0.016 µg/ml, respectively, and is still present in the blood after 24 hours (0.007 µg/ml).

Figure 1 compares the time course of the serum concentrations obtained in the two different groups of patients.

It can be observed that there are no significant differences between the two groups studied, neither regarding the concentrations nor the time course.

DISCUSSION

This study has shown that the administration of benzydamine as a vaginal douche produces similar serum concentrations in patients with and without vaginal inflammation. This result indicates that an inflammatory condition of the vaginal mucosa does not significantly influence the systemic absorption of the drug.

Table 3. — *Serum concentrations of benzydamine obtained by different routes of administration.*

Administration	Dose in mg/kg	Peak serum concentration µg/ml	Correlation index *
Oral	1.4	1	100
Cream	1.4	0.2	20
Mouthwash	1.4	0.06	6
Vaginal douche	2.4	0.02	2

* Calculated by making the oral peak serum concentration equal to 100.

The highest concentrations of benzydamine found in the blood after vaginal douching are 0.02 μg/ml. In order to facilitate the evaluation of this result, table 3 compares the peak serum concentrations of benzydamine obtained by different routes of administration used in therapy.

The highest serum concentrations are reached after oral administration: they are of about 1 μg/ml ([30, 31]). The cream produce a therapeutic effect because of benzydamine's local action and not because of its systemic absorption; they therefore constitute a means of rendering benzydamine more specific, minimizing its systemic effects.

To complete the comparison between the different routes of administration of benzydamine, figure 2 reports the relative time course of its serum concentrations.

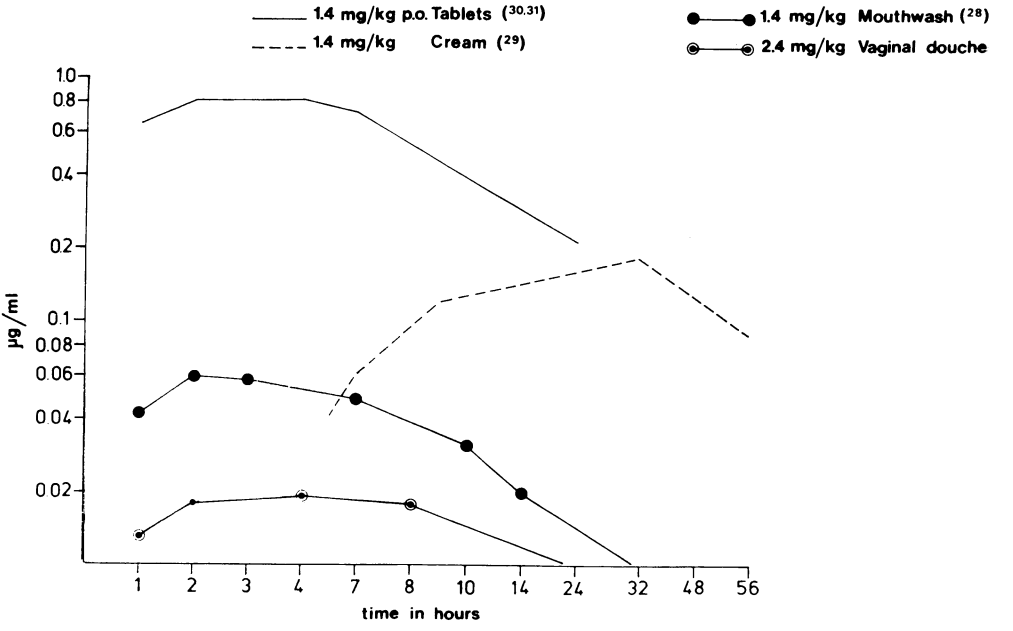

Fig. 2. — Time course of serum concentrations obtained with various forms of administration.

duces concentrations of 0.2 μg/ml ([29]), i.e. five times lower than those obtained by the systemic route. The serum concentrations obtained with the mouthwash are 0.06 μg/ml ([28]). The lowest serum levels are produced by the vaginal douche. Even though there is no direct comparison of the clinical effectiveness of these various forms of administration, it may be argued that they produce substantially similar therapeutic effects. Consequently, these data demonstrate that the topical forms

Under this aspect, the cream appears the form which is able to produce the most prolonged effects. This result suggests that with the cream the systemic absorption of benzydamine may play a significant role in its therapeutic effectiveness. As far as the other topical forms are concerned, the serum levels have a similar course to that obtained after oral administration.

In conclusion, these data on the whole demonstrate that the poor absorption ob-

served with the administration of benzydamine by vaginal douche excludes the possibility of eventual effects of accumulation and the risk of undesired systemic side effects. Moreover, they further confirm that the topical uses represent benzydamine's best mode of administration for all inflammatory conditions of the skin and mucous membranes which can be reached by this type of treatment. In fact, they provide as effective a therapy as by the systemic route but a more selective one, capable of reducing to a minimum the risk of possible side effects.

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