Acta Dermatovener (Stockholm) 50: 466–468, 1970

CLINICAL EVALUATION OF BENDAZAC (AF-983)

A Non-steroid Topical Anti-inflammatory Agent

M. de Gregorio and P. L. Meneghelli

From the Dermatological Clinic of the University of Milan, Milan, Italy

Abstract. One controlled and one open clinical study have successfully been performed with a new anti-inflammatory agent: bendazac. This compound is not a steroid, and its action is mainly due to its ability to prevent the protein denaturation which accompanies the inflammatory process. Bendazac has a specific topical action and no systemic effect.

Recently, studies in animals outlined the local anti-inflammatory properties of 1-benzyl-indazole-3-oxyacetic acid (AF-983 or bendazac) and showed important differences between this compound and hydrocortisone based on the following observations: it exerts a potent contact action devoid of any systemic effect, is active on necrotic components of inflammation, and does not interfere with proliferative and defensive processes of skin (6). Its mechanism of action has been related to its protective effect against protein denaturation (5).

In our study an attempt was made to assess the potentialities of the compound as an effective dermatological remedy in man and to compare it with the above-mentioned drugs. This paper presents the results of double-blind, paired comparison trials of topical application of bendazac and hydrocortisone or placebo in treatment of eczema. Experience with bendazac in more extensive clinical use is also reported.

MATERIAL AND METHODS

Double-blind studies in eczema

The double-blind, simultaneous paired comparison technique (with randomization of the R and L tubes among the pairs in each series) was employed and the following two comparisons were made: (*a*) 3% bendazac against placebo, and (b) 3% bendazac against 3% hydrocortisone acetate.

Both hydrocortisone acetate and bendazac were supplied in 50 g tubes, in a conventional, creamy vehicle (o/w emulsion); the plain vehicle was utilized as the placebo.

Only patients with eczematous eruptions which might be expected to respond to the application of a steroid cream, and which were symmetrically distributed, were admitted to the trial.

Symmetrical areas with almost equivalent disease involvement were chosen for study.

Applications were made twice daily without occlusion.

Follow-up examinations were performed daily over a period of 5 to 14 days. Each patient was both objectively examined and subjectively questioned. Each evaluation was recorded on appropriate report forms. Upon completion of the experimental treatment an overall evaluation was expressed as to which studied area showed greater clinical improvement, if any.

Furthermore, as soon as each patient's trial was concluded, the result of the comparison between creams was decoded. Patients in whom there was no detectable difference in the responses to the two creams were defined tied-pairs. The remaining results were recorded each time on a restricted sequential analysis graph (1). A design was chosen which was designated by the factors $2\alpha = 0.01$, $1\beta = 0.95$, $\theta = 0.85$.

By this means a trial could be terminated as soon as a statistically significant result was achieved.

A group of 19 adult patients were included in the double-blind, paired comparison trial made with the first series of tubes (3% bendazac against placebo).

A total of 24 adult patients were admitted to the trial in which the second series of tubes was utilized (comparison of 3% bendazac against 3% hydrocortisone acetate).

Clinical use of bendazac (Open study)

3% bendazac cream was evaluated on 44 patients of both sexes affected with various acute or subacute dermatoses, mostly of the eczematous type.

Application was made twice daily covering the lesion with a fine layer of cream and then with a non-occlusive protective dressing which was left in place for not less than 8 hours. Before each application the lesion was cleaned with physiological solution, or, when pyodermization was present, with slightly anti-septic solution (boric

acid, permanganate, quaternary ammonium solution etc.). No other topical drugs were used. In some cases vitamins and antibiotics were administered by systemic route, but no antihistaminic or anti-reactive agents were used which could modify symptoms and signs.

Average duration of treatment was 7–8 days, with a minimum of 5 days and a maximum of 12 days.

In order to evaluate the effect of the drug the following symptoms and signs were examined: erythema, edema, vesiculation, weeping, scaling, infiltration, itching, burning, as well as other symptoms present in some cases only. Observation was made daily always by the same experimenter.

The final clinical result was considered "excellent" when a total or almost total regression of all symptoms was observed; "good" when regression was total or almost total for some symptoms while for others it reached 70–80%; "fair" when all symptoms were favorably influenced and the entity of their regression was generally around 50%; "poor" when only some symptoms had moderately subsided; "nil" in absence of improvement or in presence of deterioration. In this final case experimental treatment was immediately suspended.

RESULTS

Double-blind studies in eczema

In the trial in which 3% bendazac was compared with placebo the statistically significant boundary at the 1% level was reached after 18 non-tied pairs had been recorded and the result indicated that 3% bendazac cream was more effective than its unmedicated vehicle.

In one patient no difference between bendazac and placebo was observed and both formulations worked well.

Two patients responded better to the unmedicated cream than to the medicated one.

In the remaining 16 the superiority of the bendazac cream was clearly seen.

In the trial in which 3% bendazac was compared with 3% hydrocortisone acetate the "no significant difference" boundary was reached when 21 non-tied pairs had been recorded.

In 3 patients the results with the two formulations were equally good.

Eleven patients showed a preference for hydrocortisone; in 7 of these the result with bendazac was good.

The remaining 10 patients showed a preference for bendazac.

Clinical use of bendazac (Open study)

35 patients suffering from eczema and 9 patients with other dermatoses were treated with bendazac 3% cream twice a day for 5–12 days.

(*a*) Tolerance to 3% bendazac cream was generally good. Only in 3 cases were signs of intolerance noted, marked by an increase of erythema and vesiculation and by symptoms of itching and burning.

(*b*) In 7 cases favorable action on symptoms was shown by an almost complete subsidence of all dermatosis elements at an early stage (excellent result). In 16 cases 60–80% disappearance of some symptoms and a good reduction of others was obtained (good result). Altogether "excellent" and "good" results represent 52% of the cases.

In another 15 subjects (34% of the cases) clinical improvement was fair. In the remaining 6 patients (14%) results were slight in 3 cases and nil in 3 cases due to intolerance.

The therapeutic effect of the drug was particularly evident in the following symptoms: erythema, edema, itching and scaling.

In conclusion, 3% bendazac cream has displayed, besides good tolerance, a satisfactory anti-inflammatory activity in most of the cases treated, has brought a considerable percentage of the cases treated to normal, and has a good soothing action on itching.

DISCUSSION

Pharmacologic investigation has shown that bendazac has a topical anti-inflammatory action while lacking any significant activity following systemic administration; the latter feature has been correlated to the low levels reached in the blood (6). It has been suggested that the anti-inflammatory activity of bendazac is associated with its anti-denaturant action on proteins, an action completely different from that of the steroids (5).

The first clinical results with the use of bendazac in man have indicated that the drug has actual effectiveness as a topical remedy in venous leg ulcers (2, 4) and in various forms of eczema (3, 7).

Our findings in the present study confirm the results already obtained and show that bendazac, at a concentration of 3%, has an anti-inflammatory activity which is approximately equivalent to that of 3% hydrocortisone acetate.

REFERENCES

1. Armitage, P.: Sequential Medical Trials. Blackwell Scientific Publications, Oxford, 1960.

2. Bassetti, F., Valenzano, L., Valenzano, G. & De Gregorio, H.: Ricerche cliniche sull'attività dell'acido bendazolico, un nuovo anti-infiammatorio di contatto non steroideo. Effetti su diversi tipi di ulcera delle gambe. G Ital Derm Min Derm *44:* 192, 1969.
3. D'Angelo, I.: Considerazioni sull'impiego dell'acido bendazolico in dermatologia. Report to 49th Int. Congr. S.I.D.E.S., Roma, 1968.
4. Nazzaro, P., Bassetti, F., Damiani, S., De Gregorio, M. & Peruzy, A. D.: Clinical testing for the evaluation of a drug in the treatment of chronic leg ulcers. Report to 4th Symposium on Dermatology, Czechoslovak Derm. Soc., Olomouc, 1968.
5. Silvestrini, B., Catanese, B. & Lisciani, R.: A biochemical basis of the anti-inflammatory activity of bendazac (AF-983). Symposium on Inflammation Biochemistry and Drug Interaction, Como, 1968.
6. Silvestrini, B., Cioli, V. & Burberi, S.: Pharmacological properties of bendazolic acid (AF-983) with particular reference to its topical action on some experimental inflammatory processes. Arzneimittel-Forschung *19:* 30, 1968.
7. Zar, E. & De Gregorio, M.: Valutazione clinica di un nuovo antiinfiammatorio topico: l'acido bendazolico (bendazac). Report to 49th Int. Congr. S.I.D.E.S., Roma, 1968.

Received October 2, 1969

P. L. Meneghelli, M.D.
Clinica Dermatologica dell'Università
Via Pace 9
Milano
Italy