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The Treatment of Lepromatous Leprosy and Erythema Nodosum Leprosum with the Cytostatic Drugs Ancyte* and Vercyte*

E. J. SCHULZ, M.MED., D.P.H.
Research Assistant, Westfort Institution, Pretoria, and
Lecturer in Dermatology, University of Pretoria

GEOFFREY FALKSON, M.D.†
Senior Cancer Chemotherapist, Pretoria

INTRODUCTION

Having carried out clinical trials on the immunosuppressive effects in leprosy of cytostatics such as cyclophosphamide (Davison *et al.*, 1964) and procarbazine (Schulz and Falkson (*a*) 1965, (*b*) 1965, (*c*) 1966), we decided to investigate the effect of 2 new cytostatic piperazine derivatives on erythema nodosum leprosum.

Vercyte (A-8103 or N,N^1-Bis (3 bromopropionyl) piperazine) is a neutral amide. The halogens in this compound are not particularly reactive in contrast with the halogens in the nitrogen mustards. Ancyte (A-20968 or N,N^1-bis (3 methane sulfonyloxypropanoyl) piperazine) is an analogue of Vercyte and is also a neutral amide. These compounds differ in structure from other previously used anti-cancer drugs. They both show marked anti-tumour effect in animals and man. Although both agents have myelosuppressive effect at the dosage used in this study these effects develop slowly and are quickly reversible.

MATERIALS AND METHODS

Six patients with lepromatous leprosy with erythema nodosum leprosum were treated with Vercyte followed by Ancyte. All 6 patients had had severe continuous ENL despite corticosteroid administration for from 15-36 months before treatment was started. Corticosteroid treatment was continued throughout the period of treatment with Vercyte and Ancyte.

One mgm. per kg. per day of Vercyte was given to the patients for 5 weeks. Three and a half weeks after the Vercyte was stopped 2.5 mgm./kg. of Ancyte was given 3 times a week for 13 weeks to 5 patients (Nos. 1, 3, 4, 5 and 6) and for 4 weeks to one patient (No. 2). The drugs were given by mouth. Blood counts were done at weekly intervals. The age, sex, total dose of Vercyte and Ancyte, lowest white cell count during treatment with the 2 drugs are given in Table 1.

The duration of standard antileprosy treatment before the piperazine derivates were given is shown in Table 1. It can be seen that treatment had in one instance already been given for 5 years. During the treatment with Vercyte and Ancyte treatment with sulfone was continued in 5 patients (Nos. 1, 2, 3, 4 and 6) and thiambutosine in one patient (No. 5).

Bacterial indices were done at monthly intervals.

RESULTS

During the 5 weeks treatment with Vercyte no significant decrease was observed in the occurrence of erythema nodosum leprosum. No toxic effects attributable to Vercyte were

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TABLE 1

Details of Treatment with Ancyte and Vercyte

No.	*Age*	*Sex*	*Duration of Previous Treatment in months*	*Total dose Vercyte in mgm.*	*Lowest White cell count on Vercyte per mm.*^{3}	*Total dose Ancyte in mgm.*	*Lowest White cell count on Ancyte per mm.*^{3}
1	35	M	51	2040	4700	5850	5050
2	42	M	22	1800	6450	2062.5	5830
3	49	M	46	2160	6000	5850	5750
4	15	M	26	1260	7150	3900	7000
5	12	M	65	1260	6000	3900	5900
6	27	M	31	2160	5000	5850	5100

encountered. None of the patients became leukopenic but the average white cell count decreased from 10,800 to 6,850 per mm.^{3} In the $3\frac{1}{2}$ weeks observation periods following discontinuation of Vercyte, most patients experienced a worsening of the ENL, despite the fact that there had been no significant improvement on treatment.

During treatment with Ancyte for 12 weeks in 5 patients and 4 weeks in one patient, all 6 patients continued to develop new ENL. Patient No. 2 complained of weakness and dizziness which he ascribed to the drug, which was stopped at his request. The symptoms disappeared 2 weeks after the Ancyte was stopped. Neither subjective nor objective side effects occurred in the other patients. The average white cell count at the start of Ancyte administration was 9,500 and at the end of treatment was 10,900 per mm.

All 6 patients continued to suffer from the same amount of ENL during treatment and as the reactions continued to be severe it was considered that a trial of longer than 3 months was not justified. An interesting observation was, however, that 3 patients had a severe exacerbation of the ENL after the Vercyte was stopped and before the Ancyte was started.

There was no significant change in the bacterial indicies before and after the administration of Vercyte and Ancyte.

DISCUSSION

Clinical and bacteriological response to dapsone may only follow after years of treatment in lepromatous leprosy. Erythema nodosum leprosum develops in 30% of our lepromatous patients. We reported suppression of acute reactions in 5 out of 8 patients who were treated with large intravenous doses of cyclophosphamide together with dapsone (Davison *et al.*, 1964). None of 9 patients treated with small oral doses of cyclophosphamide for up to 146 days and none of 6 patients treated with small oral doses of procarbazine for up to 36 weeks (Schulz and Falkson, 1965a) showed a decrease in ENL. Both cyclophosphamide and procarbazine suppress immune response. Therapeutic response to cyclophosphamide and procarbazine in cancer is seldom adequate unless a concentration of the drug, high enough to cause leukopenia is achieved. Drug concentration of this order was not considered justified in a non-malignant disease.

The dosages of Vercyte and Ancyte used in this trial are the same as those originally recommended in clinical cancer trials. These doses did not cause leukopenia in our patients with leprosy. The combination of Vercyte with corticosteroids can cause sudden and severe leukopenia in patients with blastic transformation in acute myeloid leukemia (van Dyk *et al.*, 1967). The total dose of Ancyte and Vercyte administered during 21 weeks is considered adequate for evaluation in our trial and we conclude that at this dosage range no beneficial effect is obtained in ENL. Higher doses are not considered justifiable in the treatment of ENL because of the possibility of thrombocytopenia and severe diarrhoea.

SUMMARY

Six patients with lepromatous leprosy and severe recurrent ENL were given a course of treatment first with Vercyte and after a $3\frac{1}{2}$ weeks break with Ancyte. No significant side effects were encountered and no therapeutic benefit was observed. After withdrawal of Vercyte 3 patients had severe exacerbations of ENL.

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