INDOMETHACIN IN THE TREATMENT OF ERYTHEMA NODOSUM LEPROSUM, IN COMPARISON WITH PREDNISOLONE

By Tong Hoo Ing

Erythema Nodosum Leprosum (henceforth referred to as ENL) is a well known complication in lepromatous patients during Chemotherapy and may require a decrease in dosage, or if severe, withdrawal of the drug for a period of time. The above statement appears in the report of the 7th International Congress of Leprology (1958).

Murata (1912), who was the first to coin the name "erythema nodosum leprosum", pointed out that the attack appeared with manifestations of fever, sometimes accompanied by rigor, at other times it was non-febrile. The eruption appeared mostly on the face, as well as on the flexor surface of the limbs. It was mentioned that the pathology was that "of an inflammatory formation with fatty tissue, of infiltrating colonies of poly morphonuclear leucocytes."

ENL, then, is an acute condition and has been described under the terms 'rose-spot nodules', 'acute lepra reaction' (Cochrane, 1947), and in its sub-acute form as 'panniculitis nodosa'. (Pepler, Kooij, and Marshall, 1955).

The majority of workers support the view that ENL is probably an example of bacterial allergy and that it represents "a pattern of allergic reaction to organisms in situ, or to drugs or toxins carried by the blood stream" (Ingram and Brain, 1957). It is a specific condition both clinically and histologically different from the classic erythema nodosum (Petit and Waters, 1967).

The drugs which have been used in Trafalgar Home in treating ENL are:

1. Trivalent Antimony Compounds, in particular Stibophen.
2. Chloroquin Sulphate
3. The Corticosteroids, mainly Prednisolone.

The antimony compounds have to be given parenterally, and the patients have found the Stibophen injections to be very painful. Furthermore, the possibility of liver damage prohibits the use of these compounds for too long.

Although several workers have given favourable reports on the use of Chloroquin in the treatment of ENL (Ramanujam, 1960), Chloroquin has not proved effective in the experience of Cochrane (1964), and in our experience in Trafalgar Home.

The corticosteroids, in particular, Prednisolone, have been the mainstay in the treatment of ENL in Trafalgar Home. However, numerous side effects had been encountered with its prolonged use including mooning of the face, oedema, hypertension, diabetes mellitus, osteoporosis, secondary infections, and peptic ulceration.

Thus it can be seen the need for a non-steroid drug to treat ENL is very pressing. Sheskin (1965) attempted to use Thalidomide in lepra reaction, but the teratogenicity of this drug makes one rather wary in using it in such a common condition in leprosy as ENL. Petit (1967), in a controlled study, found that B.663, a riminophenazine compound, had no anti-inflammatory effect in ENL.

Indomethacin is a non-steroid anti-inflammatory agent with analgesic and anti-pyretic properties. Clinically, Paul and Strottman (1963), and Ballabio et al (1963) reported promising results from the use of Indomethacin in the treatment of Chronic rheumatic disorders, and Smyth et al (1963) obtained dramatic results in Gout. There has been no report on its use in the treatment of ENL.

Therefore, in the absence of an effective non-steroid drug, it was decided to investigate whether or not Indomethacin had any effect on patients with ENL, and to compare its efficacy with the established Prednisolone.

MATERIAL FOR STUDY

Between October 1966 and May 1967, 30 cases of lepromatous leprosy who reported with ENL of mild, moderate and severe degrees, were accepted for the investigation.

THE METHOD

The cases for investigation were entered on a proforma together with the details of the patient's condition, such as the drug he was on, the onset of the reaction, its severity, and also the symptoms and signs such as pain, tenderness, fever, presence of rose-spot nodules, sub-

cutaneous nodules and joint swelling. Details of treatment given and the progress of the case from time to time was recorded.

Patients were given either Indomethacin 25 mg. three times daily, or Prednisolone 5 mg. three times daily, for one month. The patients were allocated at random so that about half received one drug and the remainder the alternative preparation. Should the symtoms and signs disappear completely before one month, the drug was tailed off and discontinued.

The assessment of the severity of the ENL is based on the classification given by Waters (9):

1. Mild, causing little discomfort and responding to standard therapy.
2. Moderate, normally persistent, and not easily controlled by standard therapy. May be controlled by 5 to 15 mg. Prednisolone daily.
3. Severe, persistent, causing very considerable discomfort, unaffected by standard therapy, and requiring 20-35 mg. Prednisolone for adequate control.

Laboratory investigations included estimation of haemoglobin level, total leucocyte count and erythrocyte sedimentation rate (Westergren), which were done at the start and finish of the study.

All patients were seen at least twice weekly for assessment, and also to note if the patient had experienced any side effects.

Points were allotted according to the following scheme;

Definite improvement	+2
Variable, on the whole better	+1
No change	0
Variable, on the whole worse	—1
Definitely worse	—2

Improvement or deterioration was judged by comparison with descriptions of the severity of the reaction prior to the study. The points obtained for relief of pain and for subsidence of ENL lesions, are calculated separately.

The index of clinical effectiveness is calculated thus:

$$\text{Index of clinical Effectiveness} = \frac{\text{Total number of points obtained}}{\text{Maximum points obtainable}} \times 100$$

This index is calculated separately for the different degrees of severity.

Anti-leprosy drugs were given as usual during the four week trial period and no additional analgesics were prescribed.

RESULTS

Indomethacin was used in 3 patients with severe ENL, 4 with moderate ENL, and 9 with mild ENL, whereas Prednisolone was used in 3 severe, 5 moderate and 6 mild cases.

Thus 16 patients were put on Indomethacin and 14 on Prednisolone.

TABLE I

PRETREATMENT FINDINGS

Treatment:	Number of Patients	
	Indomethacin	Prednisolone
Degree of Severity:		
Mild	9	6
Moderate	4	5
Severe	3	3
Painful Nodules	12	9
Average E.S.R.	54,2mm	38.11mm
Average Hb.	81.36%	86.88%
Average leucocyte Count	7,200	6,900

Table 1 gives the pretreatment findings. A study of this table reveals that the treatment groups are comparable with respect to number of patients in each grade of severity, number of patients with painful nodules, haemoglobin level and leucocyte count, but they were not very similar with respects to the ESR. This however can be safely ignored, especially as patients have been used as their own controls and the analysis has been concerned with the changes that occurred in the patients, condition over the period of the trial.

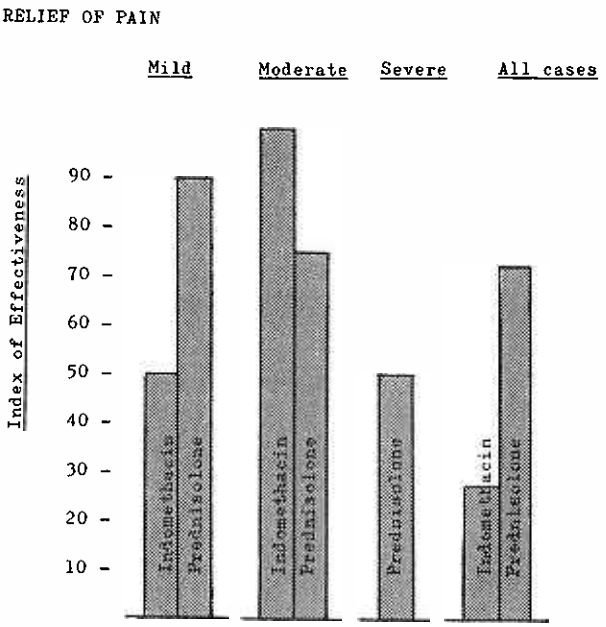


Table 2 gives the mean changes in each factor from week 0 to week 4.

TABLE II

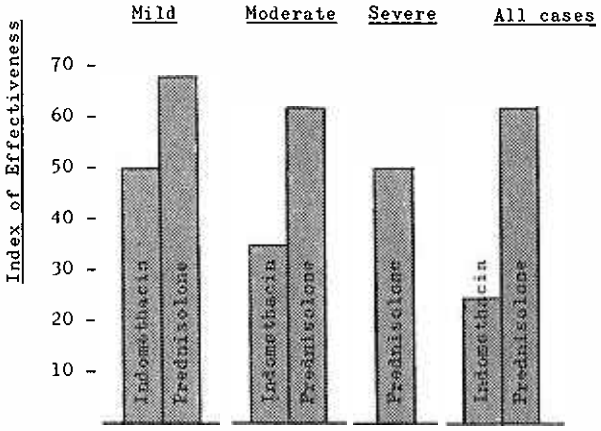
RESULTS OF ASSESSMENT DURING 4 WEEKS OF TRIAL

Treatment:	Number of Patients	
	Indomethacin	Prednisolone
Pain Relieved completely	7	6
Pain not relieved	5	3
Complete Subsidence of Lesions:		
Mild	6	2
Moderate	2	1
Severe	0	0
Partial Subsidence of Lesions:		
Mild	1	4
Moderate	1	3
Severe	0	3
No change or worse		
Mild	2	0
Moderate	1	1
Severe	3	0
Average E.S.R.	57.10	21.22
Average Hb	80%	85.6%
Average leucocyte Count	7,600	6,400

The graph for Indomethacin in the Severe group is not shown because the Index is negative. It can be seen that in the Mild and Moderate cases of ENL, the analgesic effect of Indomethacin is comparable to that of Prednisolone in the dosages prescribed. However, in the Severe Cases, Indomethacin did not bring about a response. In fact all the 3 cases on Indomethacin became worse. On working out the Index of Effectiveness for all cases, the Index for Indomethacin is less than half that of Prednisolone.

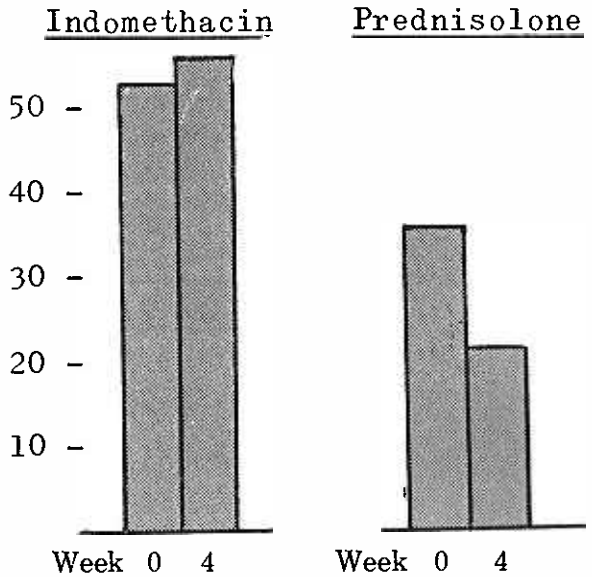
Subsidence of Cutaneous and Subcutaneous Nodules

One case in the Severe Group on Indomethacin did not complete the 4 week course as his condition had deteriorated and the nodules developed pustulation.



Here again, the graph for Indomethacin in the Severe Group is not drawn because of the negative value of the Index of Effectiveness. In mild cases of ENL, Indomethacin can be considered to have equivalent potency to Prednisolone in respect of anti-inflammatory action. In Moderate Cases, Indomethacin did exert same effect, although somewhat less than Prednisolone. In the Severe cases, there was deterioration in the patients who had Indomethacin. Again the Index for all cases for Indomethacin is about one-third that for Prednisolone.

ERYTHROCYTE SEDIMENTATION RATE



It can be seen from the graphs that the E.S.R. rose slightly (by 3mm) during the period when Indomethacin was given, while Prednisolone brought about a significant reduction in the E.S.R. (by 16.9mm) during the 4-week trial period.

Haemoglobin Level Total Leucocyte Count

There was no significant reduction in these factors with either drug.

Side Effects

Table 3 shows the more important side-effects observed and their incidence.

TABLE III

INCIDENCE OF SIDE-EFFECTS

Side-effect	Number of Patients	
	Indomethacin	Prenisoloned
Nausea	4	0
Vomiting	1	0
Dizziness	3	0
Epigastric pain	0	1
Insomnia	1	0
Total Side-effects	9	1

DISCUSSION

In attempting to evaluate drug treatment of ENL, one must be aware of its fluctuant nature and its wide range of clinical severity. The drug of choice is one which relieves pain, brings about a subsidence of cutaneous and subcutaneous nodules, and has minimal unimportant side-effects. So far, no drug has satisfied all these criteria.

In the above study, painful symptoms were experienced in 21 cases, 12 in the Indomethacin group and 9 in the Prednisolone group. Indomethacin relieved pain in 7 cases, all of whom had Mild and Moderate ENL. Prednisolone relieved pain in 6 cases belonging to all the three grades of severity. A study of the graphs show that Indomethacin, although inferior to Prednisolone is useful in the treatment of patients with Mild and Moderate ENL.

In the suppression of cutaneous and subcutaneous nodules, the results almost parallel those for the relief of pain. Indomethacin brought about complete subsidence in 6 Mild cases, and in 2 Moderate cases; partial subsidence in 1 Mild and 1 Moderate case. There was no improvement in 2 Mild cases and 1 Moderate case, while all the 3 Severe cases became worse while on Indomethacin. Prednisolone brought about complete subsidence in 2 patients with Mild ENL, 1 patient with Moderate ENL; partial subsidence in 4 cases with Mild ENL, 3 with Moderate ENL, and 3 with Severe ENL. One case with Moderate ENL showed no change.

Here again, a study of the graphs reveals the superiority of Prednisolone in the suppression of ENL, but Indomethacin does exert a significant effect in bringing about subsidence on nodules in Mild and Moderate cases of ENL.

The Erythrocyte Sedimentation Rate rose by 3 mm. in the group which had Indomethacin. Bain and Masheter (1966), also noted such a rise in their double-blind controlled trial in which they compared Indomethacin and Flufenamic acid in the treatment of Rheumatoid Arthritis. Prednisolone caused a significant fall in the E.S.R., from an average of 38.1 mm. to 21.2 mm.

The haemoglobin levels and total leucocyte counts did not show significant changes in both treatment groups.

6 patients (37.5%) experienced 9 undesirable side-effects from Indomethacin. The most frequent side-effects were nausea and dizziness. These were transient and occurred within the first few days of starting treatment. In the Prednisolone group, only 1 patient had epigastric pain, which occurred towards the end of the trial period. In comparing side-effects, one must bear in mind that one month is too short a time to observe the side-effects from Prednisolone, as these tend to manifest themselves only after prolonged usage.

SUMMARY AND CONCLUSIONS

The results of a one-month clinical trial in the treatment of ENL, comparing Indomethacin (75mg. daily) and Prednisolone (15mg. daily) are reported. Overall benefit was obtained in 60% on Indomethacin, and 75% on Prednisolone.

Indomethacin is effective in treating only Mild and Moderate cases of ENL. There was no improvement in the E.S.R. with Indomethacin.

Side-effects occurred in 37.5% of patients in the Indomethacin group. The common side-effects were nausea and dizziness. Only 1 patient on Prednisolone experienced epigastric pain.

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