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Indomethacin in the Management of Erythema Nodosum Leprosum—A Double-blind Controlled Trial*

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This investigation of the efficacy of indomethacin in comparison with 3 other drugs (prednisolone, chloroquine, and aspirin) in the management of exacerbations of lepromatous leprosy (ENL) has shown that indomethacin and chloroquine were the most useful in decreasing the number of recurrences and that indomethacin was the most beneficial in improving vision but was no better than the other drugs in regard to arthralgia, acute exudative arthritis, and acute painful neuritis.

INTRODUCTION

Indomethacin is an indole derivative which was first synthesized in 1961 and found to have anti-inflammatory properties. It is a non-steroidal drug and is unrelated to any other known anti-inflammatory agent. Calculations based on animal tests have shown the drug to be between 10 and 85 times as potent as hydrocortisone (Winter *et al.*, 1963).

Clinical trials have demonstrated that indomethacin has anti-inflammatory, anti-pyretic, and analgesic properties when administered to patients with rheumatoid arthritis, osteoarthritis, and gout (Hart and Boardman, 1963; Smyth, 1965; Morkel, 1966). The results achieved by the use of the drug in these conditions have been encouraging.

While the role of steroids in the management of severely exacerbated phases of leprosy is well established their long-term use is hazardous, and the search for an alternative drug has to be continued. An open trial of indomethacin in our hospital gave encouraging results (Thomas *et al.*, 1968), and to further evaluate more fully its efficacy in the management of exacerbations in lepromatous leprosy, a double-blind controlled trial was carried out using prednisolone, indomethacin, chloroquine, and aspirin; from their initials the trial was known as "PICA" and this word was written on prescriptions ordered for patients entering the trials. The specific objectives of this study were to collect unbiased data on: (1) the role of indomethacin in controlling exacerbations of lepromatous leprosy, specifically erythema nodosum leprosum, fever, arthritis, periostitis, neuritis, iritis, lymphadenitis, and oedema; (2) its value in preventing further exacerbations while the patient was receiving maintenance doses of the drug; (3) the possibility of the early re-introduction of specific anti-leprosy therapy, following control of the exacerbated state, without precipitation of further attacks of exacerbation; and (4) the side-effects, if any, encountered during administration of the drug.

MATERIALS AND METHODS

During the 6-month period between November 1967 and May 1968, all lepromatous leprosy

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patients admitted to the Schieffelin Leprosy Research Sanatorium for control of exacerbation ("reaction" with erythema nodosum leprosum (ENL)) were screened and accepted for the trial provided that they were over 12 years of age, had no history or radiological evidence of peptic ulceration, pulmonary tuberculosis, hypertension, diabetes, severe intercurrent infection, or exacerbation associated with acute peripheral nerve paralysis, and no medical condition requiring the use of other anti-leprosy agents, such as long-acting sulphonamides or streptomycin. On admission to the trial, all specific anti-leprosy drugs were stopped. Each patient admitted to the trial was given a serial number and treated with one of the 4 drugs according to a confidential, randomized list. The Nursing Superintendent was responsible for the dispensing of drugs according to the therapeutic régimes shown in Table 1.

All drugs were administered orally at meal times, indomethacin being given in 25 mg capsules, aspirin in the form of "Ascriptin" tablets (aspirin 5 gr, with magnesium aluminium hydroxide 2.5 gr), chloroquine as 250 mg tablets, and prednisolone as 5 mg tablets. During the exacerbated phases, restless patients were sedated with phenobarbitone, 60 to 90 mg at night, or with chlorpromazine ("largactil") 25 mg t.d.s. by day as needed. No anti-inflammatory agents other than "PICA" were prescribed and diuretics were prescribed only when oedema was progressive and obviously uncontrolled by "PICA"; appropriate clinical notes were made by the observer-clinician at the time. Specific anti-leprosy treatment (dapsone) was re-introduced only when a patient was free of symptoms of reactions for at least 4 weeks.

A total of 50 lepromatous patients were included in this study, of whom 13 received prednisolone, 11 indomethacin, 12 chloroquine, and 14 Ascriptin. The clinical status of each patient was assessed on admission and graded according to the system shown in Table 2.

Table 1
Therapeutic régimes

Drug	*Dosage*		
	First 2 weeks	*Third week*	*Maintenance*
Prednisolone (P)	5 mg t.d.s.	5 mg b.d.	5 mg o.d.
Indomethacin (I)	50 mg t.d.s.	25 mg t.d.s.	25 mg o.d.
Chloroquine (C)	250 mg t.d.s.	250 mg b.d.	250 mg o.d.
Aspirin (A)	1 g t.d.s.	1 g b.d.	0.5 g b.d.

Table 2
Grading of reactional status

Grade		*Symptoms and signs*				*Oral temperature (°F)*
		Subcutaneous nodules	*Periosteitis neuritis and arthritis*	*Oedema*	*Others*	
1+	Few; superficial; not tender	Nil	Pain but not tenderness	±Minimal		99.0–101
2+	Scattered; mostly superficial; a little tender	±	With some tenderness	±Moderate		99.0–103
3+	Multiple; superficial and deep; painful and tender	±Tender	Painful and tender	±Gross	±Iritis ±Tender and painful lymphadenitis	99.0–105
4+	Multiple; superficial and deep; very painful and tender; nectrotic	±Tender	Very painful and tender	±Gross	Iritis; very painful and tender lymphadenitis; toxic state with distress	99.0–105

Clinical assessments were made on alternate days throughout the acute period and thereafter at monthly intervals until the trial period of 90 days had been completed.

The distribution of patients in each drug group according to the severity of presenting symptoms is shown in Table 3. Personal experience has led us to the belief that exacerbations of Grades 1 and 2+ differ from those of Grades 3 and 4+, not only in their clinical features but also in the degree of systemic disturbance which they cause and their response to anti-inflammatory drugs. It has thus been found convenient to discuss the findings in Grades 1 and 2+ as one category and Grades 3 and 4+ as another.

TABLE 3
Distribution according to severity of exacerbation in each drug group

Drug group	*Reaction*				*Total*
	Mild		*Severe*		
	1+	2+	3+	4+	
P	1	11	–	1	13
I	–	5	1	5	11
C	–	6	2	4	12
A	2	3	4	5	14
Total	3	25	7	15	50

It is somewhat unfortunate that by chance the majority of patients in the less-severe reaction group were receiving prednisolone, despite the statistically randomized grouping.

RESULTS

The number and percentage of patients in whom the reaction was successfully controlled in each of the 4 groups under study are presented in Table 4. While all the patients given prednisolone showed early response, the overall response to indomethacin was only 64%, which was not significantly different from that obtained in the chloroquine and aspirin groups. Among those who had severe exacerbations (3 or 4+) there was a higher response to indomethacin than to chloroquine, but the difference was not statistically significant.

TABLE 4
Responses to therapy in each of the 4 groups under trial

Drug group	*All cases*			*Severe cases*		
	Studied	*Responded*		*Studied*	*Responded*	
		No.	%		*No.*	%
P	13	13	100	1	1	100
I	11	7	63.6	6	4	66.7
C	12	8	66.7	6	3	50.0
A	14	10	71.4	9	5	55.6
Total	50	38	76.0	22	13	59.1

In terms of control of individual symptoms, differences were observed between the 4 drug groups, and these are shown in Table 5. None of the differences was significant statistically except in the case of neuritis, for which a significantly longer time to control the symptoms was required with indomethacin than with either prednisolone or chloroquine ($P<0.01$).

The side-effects of the various drugs were judged mainly by the subjective complaints made by the patients, except in the case of visual disturbance, where refraction studies were carried out monthly to give an objective parameter by which to judge the changes in vision. The group receiving aspirin had the least proportion (29%) of patients complaining of various side-effects, whereas 69.2% of those receiving prednisolone complained of some adverse effects. The corresponding percentages in the indomethacin and chloroquine groups were 63.6 and 58.5%. About one-quarter of the patients receiving indomethacin complained of headache, but only one complained of abdominal pain. In contrast, one-third of those receiving chloroquine complained of abdominal pain and nausea. Table 7 shows the changes in visual acuity as determined by refraction studies during the period of trial. All these patients had clinical evidence of iritis and were treated with local application of hydrocortisone and atropine eye ointment. It appears that indomethacin has a beneficial effect on vision in leprosy patients with acute iritis and iridocyclitis, and this effect appears to be greater than that of prednisolone. The recurrence of exacerbations among patients whose initial episode of ENL was controlled is presented in Table 8. This shows that the recurrence rate in the prednisolone

TABLE 5

No. of days required for the control of individual symptoms among patients in each of the 4 drug groups

(No. studied, modal values, means and standard deviations)

Symptoms	*Prednisolone*					*Indomethacin*					*Chloroquine*					*Asprin*				
	No.	*Mode*	*m*	±	S.D.	*No.*	*Mode*	*m*	±	S.D.	*No.*	*Mode*	*m*	±	S.D.	*No.*	*Mode*	*m*	±	S.D.
	11	7		±	10	6	14	15	±	3	8	7–14	14	±	11	9	7	12	±	7
Fever	8	3–5	9	±	13	4	6	14	±		8	7–9	8	±	3	8	5–7	11	±	8
Periostitis	7	7	11		12	4	7	9	±	3	4	7	9	±	3	5	7–14	14	±	8
Arthralgia	8	7	13	±		3	14	14	±	6		7	14	±	13	3	7	14	±	10
Neuritis	8	7	8	±	5	4	14	20	±	7	4	7	9	±	3	8	7		±	8
Oedema	8	7–14	13	±		4	14–21	18	±	4	8	7–14	15	±		4	21	17	±	

No., number studied; mode, modal values; m, means; S.D., standard devisions.

TABLE 6

Side-effects noticed in the 4 drug groups under trial

Drug group	*Side effects*								*Total studied*
	Abdominal pain		*Nausea*		*Headache*		*Dimness of vision*		
	No.	%	*No.*	%	*No.*	%	*No.*	%	
	2	15.4			2	15.4		7.7	13
		9.1			3	27.3			
	4	33.3	3	25.0		8.3			12
		14.2	1	7.1	3	21.3			14

and aspirin groups was nearly 70%, whereas among those given indomethacin it was only 57% and in the chloroquine group 50%. These findings were similar even among those with severe exacerbations.

As all cases receiving prednisolone showed an early initial response, patients in this group could have been restarted on anti-leprosy treatment early during the study. However, since the design of the study entailed waiting for 4 weeks after the initial response before beginning anti-leprosy therapy, the relatively early recurrence of reactions in this group meant that anti-leprosy therapy could not be introduced in all instances. In fact, in the one case of severe exacerbation in the prednisolone group no anti-leprosy drug could be introduced at all since this patient was practically continuously in reaction. Out of the 4 severe cases which responded to indomethacin, only in one case could DDS be introduced. Of the severe cases which responded to chloroquine and aspirin anti-leprosy therapy was begun in all.

TABLE 7

Changes in refraction during ' PICA' trial

Drug group	*Significant deterioration noticed*	*Significant improvement noticed*
P	4	
I		2
C		
A		
Total	7	3

TABLE 8

Recurrence of exacerbations among those who responded in each of the 4 groups under trial

Drug group	*All cases*			*Severe cases*		
	Studied	*Recurred*		*Studied*	*Recurred*	
		No.	%		*No.*	%
P	13	9	69.2	1	1	100
I	7	4	57.1	4	2	50.0
C	8	4	50.0	3	1	33.3
A	10	7	70.0	5	4	80.0

TABLE 9
Introduction of DDS in patients who responded in each of the 4 groups under trial

Drug group	*Total studied*	*Total responded*	*Among those responded DDS introduced in*	
			No.	%
P	13	13	8	61.5
I	11	7	3	42.9
C	12	8	4	50.0
A	14	10	5	50.0
Total	50	38	20	52.6

The introduction of specific anti-leprosy drugs once the exacerbation was under control was one of the criteria of the efficacy of the drug. The findings regarding this aspect are shown in Table 9; the differences were not statistically significant. The continuation of anti-leprosy therapy has depended on the recurrence of of exacerbations. Owing to the short duration of this trial, namely 12 months, and the stipulation that no anti-leprosy therapy was to be initiated until 4 weeks after control of an exacerbation, it was not possible to study the relationship between introduction of specific anti-leprosy therapy and recurrence of ENL in this group.

DISCUSSION

Lepromatous leprosy patients undergoing episodes of exacerbations present an extremely variable and difficult therapeutic problem group. The picture presented varies not only in relation to the clinical manifestations but also with the clinical course of the illness and the response to therapy observed in these cases. In any study designed to evaluate the effectiveness of an anti-inflammatory drug in lepromatous leprosy, this fact should be kept in mind; also the investigation should include a sufficiently large number of cases and means devised by which observations can be made as objective and unbiased as possible.

In this particular trial we were interested in studying the efficacy of indomethacin in the management of erythema nodosum leprosum. Choice of the controls was deliberate; though chloroquine was the chief drug for comparison, we wanted to use one very potent drug, prednisolone, and one drug which was expected to be least specific, namely aspirin. The findings as shown in the various tables are interesting and revealing. The number of cases studied was not large and in the event it so happened that the patients receiving prednisolone were, in general, in a milder grade of exacerbation than those receiving indomethacin. In spite of this advantage, the control of the exacerbations by prednisolone, though initially dramatic, was not wholly successful, in view of the early recurrences on reduction of the dosage and/or withdrawal of the drug. Comparison of the pattern of recurrences and side-effects of the 4 drugs shows that indomethacin compared favourably with the other drugs used in the trial in the dosages mentioned.

Visual disturbance was least in the indomethacin-treated patients as compared with those taking prednisolone or chloroquine. On the other hand, there was significant improvement in vision in 2 patients treated with indomethacin, while none of those in the prednisolone group showed improvement on refraction. It has been suggested that the rise in intra-ocular tension is subsequent to the use of steroids. The improvement in vision in patients treated with indomethacin could perhaps be attributed to early absorption of the plastic exudate that commonly occurs in lepromatous leprosy patients in reaction and with involvement of the eye.

The fact that symptomatic relief of painful neuritis associated with "reaction" took much longer to achieve with indomethacin than with the other drugs is somewhat surprising. Aspirin provided quicker relief in this group than did indomethacin (Table 5).

Despite the well-known effects of indomethacin in painful lesions of the joints, as for example in rheumatoid arthritis, the response of the arthralgia and acute exudative arthritis associated with ENL was less dramatic and indeed was practically the same in all 4 treatment groups.

SUMMARY

(1) A double-blind controlled clinical trial of indomethacin in the management of erythema nodosum leprosum ("reaction") and its associated clinical features was carried out, using chloroquine as the chief control drug and 2 other drugs also for comparison, namely prednisolone and aspirin. On the whole the therapeutic effect of indomethacin, in terms of its control of ENL, compared favourably with that of chloroquine and was superior to aspirin.

(2) Though initial control was most quickly achieved with prednisolone, indomethacin and chloroquine appeared to be slightly superior to the other drugs in decreasing recurrences.

(3) In regard to arthralgia and acute exudative arthritis associated with a reaction, there was no significant difference between the responses produced by the 4 drugs.

(4) Acute painful neuritis occurring in these patients appeared to respond least to indomethacin.

(5) The number of patients in whom specific anti-leprosy therapy could be reintroduced following subsidence of ENL was comparable in all 4 test groups.

(6) No significant side-effects were noted. However, there was a definite improvement in vision among the patients treated with indomethacin, while some patients receiving prednisolone showed a deterioration in vision on refraction. The significance of this difference is discussed.

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