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WHO Co-ordinated Short-Term Double-Blind Trial with Thalidomide in the Treatment of Acute Lepra Reactions in Male Lepromatous Patients*

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The treatment of lepra reactions constitutes one of the most serious problems in leprosy. For this reason, the first reports in 1965 of the favourable results obtained with thalidomide aroused considerable interest and led WHO, in 1967, to carry out a trial with the co-operation of four centres. A short-term double-blind trial was designed to study the effect of thalidomide, in comparison with acetylsalicylic acid, in the treatment of acute lepra reactions in male lepromatous patients. Acetylsalicylic acid was used instead of a placebo because of its antipyretic and analgesic activity. Because of the severe adverse reactions that may be caused by thalidomide, mainly the teratogenic effects, only males were included in the trial.

The results of this short-term study seem to confirm previous reports of the efficacy of thalidomide and indicate that acetylsalicylic acid also seems to be helpful in the management of certain symptoms of lepra reactions.

Favourable results in the treatment of lepra reactions with thalidomide were first reported by Sheskin (1965a, 1965b); improvement occurred within 48 hours of oral administration. Generally, doses of 400 mg daily were given over periods of up to 7 months. Side effects were numerous and included drowsiness, constipation, dryness of the oral and nasal mucosa, erythema of face and chest, oedema localized in one extremity, mild difficulties in erection, and vesiculobullous and eczematous rashes. In most cases these effects were transient and in no case was it necessary to withdraw the drug.

Sheskin's reports were confirmed by Sheskin & Convit (1966) in a double-blind trial. The study comprised 173 treatments, 85 using thalidomide and 88 a placebo. In the thalidomide-treated cases, there was amelioration in 91.76% and no change in 8.24%; no deterioration was observed. In the placebo-treated cases, amelioration was observed in 27.3%, no change in 50%, and deterioration in 22.7%. The authors reported that statistical analysis showed that such a result could occur by chance in fewer than one in a million cases.

In a further paper concerning the same trial, Sheskin & Convit (1969) stated:

" Improvement following thalidomide was seen after eight to 48 hours and continued steadily, although in some patients one week was insufficient for total remission of some of the symptoms.

" Before and after each treatment regimen biochemical tests, bacteriologic and histologic tests did not show any significant changes ...

" The side effects were not significant and did not influence the course of the seven-day treatment period."

Sheskin & Convit (1966) considered thalidomide to be effective against lepra reactions occurring in

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lepromatous patients. After these studies, Convit, Soto & Sheskin (1967) used the drug as a regular therapeutic agent in the treatment of 24 lepromatous patients in reactional states of different degrees; 70% of them were cases of long duration in which sulfone treatment had been suspended to prevent further aggravation of the reaction. They stated:

" Cases of acute polyneuritis incident to the reactional state were also controlled rapidly and completely under treatment with thalidomide, and the same was observed in a case of reactional iritis.

" After the disappearance of the reactional syndrome, the daily doses of the drug were reduced gradually to a maintenance dose of 50 mg. The administration of the drug, even on a maintenance level, enabled resumption of DDS treatment in cases that were formerly intolerant to sulfones. To all appearances, the problem of anti-leprosy therapy in cases subject to frequent reactions has been solved."

The secondary effects were slight. At the higher dosage rates there was some constipation, which ceased when the dose was reduced to 200 mg daily. Under prolonged treatment, oedema of the distal extremities was also observed as a temporary side effect. According to Convit, Soto & Sheskin (1967), in view of the teratogenic activity of thalidomide, treatment should be given only to hospitalized patients under strict control. Finally, after 55 months' experience with thalidomide, Sheskin (1970) stated that the optimum initial dose of thalidomide was 400 mg/day (6 mg per kg of body weight), and the optimum maintenance dose 100 mg/day. Side effects were minimal.

The preliminary results, even with smaller initial doses of thalidomide, were also confirmed by Tarabini-Castellani (1965-66, 1967) Cazort & Song (1966), Opromolla, Lima & Marques (1966), Terencio de las Aguas & Contreras (1966), Languillon, Klein & Giraudeau (1968), and many other authors.

Marques & Opromolla (1968) treated 425 cases (321 men and 104 women) with lepra reaction. In most cases, the drug was administered in daily doses of 100 mg; only exceptionally were 200 or 300 mg administered. The symptoms regressed in the following order: fever, skin lesions, and neuralgia. No striking side effects attributable to the drug were seen. Some patients complained of drowsiness, dizziness, and constipation; a few had slight oedema in one leg. With improvement of the lepra reaction, the drug was gradually reduced to a weekly dose of 100 mg before being completely withdrawn.

In the light of the earlier results, WHO decided in 1967 to study the effect of the drug and to carry out a short-term trial with the co-operation of four centres.

TECHNICAL OUTLINE

The technical outline of this short-term double-blind trial was designed in collaboration with Dr F. Sagher and Dr J. Sheskin. The technical outline was submitted to the investigators at the various centres for comments, suggestions, and approval.

Objective

The trial was designed to study the effect of thalidomide in comparison with that of acetylsalicylic acid in the treatment of acute lepra reaction in male lepromatous patients. Acetylsalicylic acid was used instead of a placebo on account of its antipyretic and analgesic activity.[1]

Co-operating centres

The following centres co-operated in the study: (1) Central Leprosy Teaching and Research Institute, Chingleput, India; (2) Institut Marchoux, Bamako, Mali; (3) Sanatorio-Villaggio Isola Alessandra, Somalia; (4) Sanatorio de Fontilles, Spain.

Criteria for inclusion of patients in the study

Dermatological criteria. Patients included in the study should have clearly demonstrable dermatological manifestations of acute lepra reactions, i.e., erythema nodosum-like lesions or erythema multiforme-like lesions. Ambulatory patients with subfebrile temperatures, with or without moderate pain but without any noticeable lowering of their general health, should be included.

Neurological criteria. Patients presenting neuritic pain and palpable evidence of neuropathy are acceptable for study.

Dangerously ill patients. Patients with severe or life-threatening lepra reactions should be treated with appropriate means; they should under no circumstances be included in the double-blind study. Patients whose clinical status during the study deteriorates to life-threatening proportions should be dropped from the study and appropriate treatment should be instituted.

[1] Jopling (1964) considered acetylsalicylic acid to be the first choice in the treatment of pain in cases of lepra reaction.

Allocation of thalidomide and acetylsalicyclic acid

Numbering of patients. Patients will be allocated consecutive numbers in the order of their admission to the study.

Allocation of drug. Patients will be treated with tablets contained in a bottle bearing their number (according to the master sheet of drug allocation). A different bottle is used for the treatment of each lepra reaction as indicated in the master sheet.

Codification. A confidential master sheet indicating the code for each therapeutic regimen and the contents of each bottle will be kept by the World Health Organization.

Breaking the code. In the event that the clinical condition of a patient requires that the code should be broken to determine the contents of an individual bottle, the number of the bottle should be telegraphed to WHO, Geneva, and the contents will be communicated by return cable. After the code is broken, the patient must be dropped from the study. Patients should also be dropped from the trial when the intake of the drug in a certain period (1st, 2nd, 3rd, or 4th bottle) is not regular.

Contents of each bottle. Each bottle will contain 31 tablets; 28 will be given to the patient, 1 tablet is to be retained at the site of the trial, 1 tablet is to be sent to WHO, Geneva, and the last tablet is to remain in each bottle for analysis in the event that an error in filling or labelling is suspected. Each tablet will contain 100 mg of thalidomide or 400 mg of acetylsalicylic acid.

Instructions to the drug manufacturer

(1) Thalidomide tablets and acetylsalicylic acid tablets will be manufactured on two separate days and on the same tableting machine.

(2) Acetylsalicylic acid tablets will be manufactured on the day before the thalidomide tablets to avoid any contamination.

(3) Each bottle will be filled with 31 tablets.

(4) Thalidomide tablets and acetylsalicylic acid tablets will be sent to: Central Leprosy Teaching and Research Institute, Chingleput, India; Institut Marchoux, Bamako, Mali; Sanatorio-Villaggio Isola Alessandra, Somalia, and Sanatorio de Fontilles, Spain.

(5) Bottles will be labelled only with numbers according to the master sheet of drug allocation.

Dosage regimen

Patients weighing 50 kg or more will receive 1 tablet 4 times a day. Patients weighing less than 50 kg should receive 1–3 tablets per day, depending upon their weight. In all cases, the drug should be given at equal intervals (e.g., 08.00, 12.00, 16.00, 20.00, when the drug is administered 4 times).

In each patient, the lepra reaction will be treated for a total of 7 days. On the 8th day, treatment of patients showing marked improvement and presenting only a subacute reaction and able to walk will stop until new acute reactions occur; tablets from the next code bottle will then be given; patients with slight, or no, improvement will immediately begin a new 7-day course of treatment as though they were suffering from their next lepra reaction. For example, if a patient treated for 7 days for his second lepra reaction does not show improvement, he immediately begins the treatment originally designed for his third lepra reaction.

Other therapy

Upon admission to the study, all drug therapy must cease.

In no circumstances should patients included in the study receive ACTH, cortisone or its analogues, antimony compounds, or antihistamines.

Patients whose clinical status makes the administration of other drugs mandatory should not be included in the study. Patients who show marked improvement should wait at least 15 days before resuming dapsone treatment. The dosage should be smaller than that used at the time the lepra reaction appeared. It may be advisable not to increase the dosage beyond the level at which the reaction appeared.

Clinical examination

A complete history should be taken and a physical examination made at the time each patient is admitted to the study. Pertinent physical findings must be reviewed at least every other day. A complete review of findings should be documented at the end of the 7-day treatment period. Photographic documentation is recommended.

Laboratory examinations

Admission. The following studies should be performed on admission to the study: blood cell count, urine analysis, blood urea nitrogen determination, erythrocyte sedimentation rate measurement, and,

if possible, SGOT (L-aspartate: 2-oxoglutarate aminotransferase, 2.6.1.1).

Serial studies. The following examinations should be performed before each therapeutic trial and on the last (seventh) day of treatment in each reaction: blood cell count, erythrocyte sedimentation rate, SGOT (if possible).

Protocol master sheets

The protocol master sheet, protocol sheets numbers 1–4 and the master sheet of drug allocation are not included in this paper but are available from Leprosy, World Health Organization, Geneva.

RESULTS

Before considering the results, it should be emphasized that the trial was a short-term one, the same patients being treated for periods of only 7 days, with either thalidomide or acetylsalicylic acid (as indicated in the dosage regimen).

Altogether, 92 patients were included in the trial. According to the random allocation, 42 patients were given acetylsalicylic acid for their first reactions and 50 were given thalidomide. The small difference in size of the two groups is explained by the fact that the randomized design provided for 100 patients and the 4 centres used different sets of random allocations from the same table.

The duration of the trial was about 9 months. During this period, 214 reactions were observed, 116 being treated with thalidomide and 98 with acetylsalicylic acid. The statistical design provided for the treatment of 4 reactions in each patient, 2 with acetylsalicylic acid and 2 with thalidomide, the order of the treatment with the two drugs being random. A total of 56 patients had less than 4 reactions during the period of the trial, and this could partly account for the unequal numbers of reactions treated by the two drugs. The distribution by age and treatment of the patients for the 214 reactions is given in Table 1. Table 2 shows the number of patients treated with the two drugs for each reaction and also shows the percentage who had 1, 2, 3, or 4 reactions.

Table 1. Number of lepra reactions treated with thalidomide or acetylsalicylic acid related to the age of the patient

Treatment	Age group					
	<15	15–24	25–34	35–44	45–54	≥55
thalidomide	0	20	59	17	8	12
acetylsalicylic acid	0	23	46	11	7	11

Table 2. Order of reaction, treatment, and number of patients with no further reaction

Order of reaction	Treatment	No. treated	No. (and percentage) with no further reaction
first	thalidomide	50	26 (52.0 %)
	acetylsalicylic acid	42	9 (21.4 %)
second	thalidomide	27	12 (44.4 %)
	acetylsalicylic acid	30	6 (20.0 %)
third	thalidomide	21	9 (42.9 %)
	acetylsalicylic acid	18	4 (22.2 %)
fourth	thalidomide	18	—[a]
	acetylsalicylic acid	8	—[a]

[a] No further information available.

It will be seen that among the 42 patients who started treatment with acetylsalicylic acid, 21% did not have any further reactions up to the end of the trial. On the other hand, among 50 patients who started treatment with thalidomide 52% did not have any further reactions. The remaining 57 had a second reaction, 30 of them being treated with acetylsalicylic acid and 27 with thalidomide; 20% of the former and 44% of the latter group did not have any further reaction. The remaining 39 patients had a third reaction; 18 were treated with acetylsalicylic acid and 21 with thalidomide. No further reactions were observed in 22% of the former and 43% of the latter. Thus there were only 26 patients left who had a fourth reaction, 8 of them were treated with acetylsalicylic acid and 18 with thalidomide.

Thus, it is clear that, at least during the period of the trial, there was on the average a 21% chance that a patient treated with acetylsalicylic acid would not show any further reactions, as against a similar chance of 48% for patients treated with thalidomide.

Table 3 shows the symptoms and signs at the start of the 214 reactions broken down according to treatment. The 116 reactions treated with thalidomide had a pattern of symptoms very similar to the

Table 3. Symptoms at initial examination

Symptoms and signs	Frequency (%) of presence in patients allocated	
	Thalidomide	Acetylsalicylic acid
pain in muscles	56.9	51.0
pain in joints	63.8	63.3
pain in nerves	52.6	49.0
malaise	61.2	60.2
insomnia	49.1	55.1
anorexia	46.6	54.1
other symptoms	31.0	29.9
temperature $\geqslant$ 37.1°	78.0	69.1
skin lesions	95.0	96.0
nerve lesions	70.7	62.2
eye lesions	16.4	17.3
lesions in the testes	21.6	17.3
lesions in the lymph nodes	57.8	48.0
lesions in the liver	27.6	19.4
lesions in the spleen	11.2	11.2

98 treated with acetylsalicylic acid. Tables 4 and 5 indicate the further similarity of the groups of reactions treated by the two drugs.

Effect on the temperature (Table 6)

From Table 6 it is observed that in the thalidomide group at the start of therapy there was a large number of cases with higher temperature ranges and that the fall of temperature was appreciably greater in this group than in the acetylsalicylic acid group. In fact, at the end of 48 hours only about 25% of the thalidomide group continued in fever while there was

Table 4. Number of lepra reactions treated with thalidomide or acetylsalicylic acid related to the number of reactions and their duration in weeks occurring in the patients during the previous 12-month period

No. of previous reactions	Th [a]	Ac [b]	Duration (weeks)	Th [a]	Ac [b]
0	26	21	0	26	21
1	20	18	1	44	37
2	24	19	2	13	15
3	11	10	3	17	13
4	16	15	4	3	4
5	8	5	5	0	0
6	2	3	6	3	1
7	0	0	7	0	0
8	1	0	8	3	3
9	8	7	9	0	0
no information			no information	7	4

[a] Th = thalidomide.
[b] Ac = acetylsalicylic acid.

64% in the acetylsalicylic acid group. It is evident that thalidomide had a striking action on body temperature.

Effect on lesions in the skin, nerves, eyes, testes, lymph nodes, liver, and spleen

Table 7 gives the status of lesions at various sites for the 214 reactions (116 treated with thalidomide and 98 with acetylsalicylic acid) at the start of treatment, and after 48 hours, 96 hours, and 8 days.

The number of reactions that were not initially attended by skin lesions was only 5.2% in the thalidomide group and 4.1% in the acetylsalicylic acid group. In the former group, the proportion with either no lesion or in an improved state after

Table 5. Number of lepra reactions treated with thalidomide or acetylsalicylic acid related to drugs taken by the patients during the previous 12 months

Treatment	Drug								
	Sulfones	Thiambutosine	ACTH	Cortisone	Antimony	Antihistamines	Antimalarials	Others	No information
thalidomide	68	0	1	4	20	2	16	87	2
acetylsalicylic acid	53	0	0	3	16	2	12	74	2

Table 6. Number of lepra reactions treated with thalidomide or acetylsalicylic acid related to temperature at initial and subsequent examinations

Time	Treatment	Temperature (°C)						
		< 37°	37.1–37.4	37.5–37.9	38.1–38.4	38.5–38.9	⩾ 39°	No information
initial	thalidomide	25	9	18	19	13	31	1
	acetylsalicylic acid	30	13	19	12	12	12	0
48 hours	thalidomide	85	14	9	2	2	3	1
	acetylsalicylic acid	35	6	15	22	11	8	1
96 hours	thalidomide	99	7	5	2	0	3	0
	acetylsalicylic acid	39	8	10	17	10	11	3
8th day	thalidomide	104	5	1	1	1	1	3
	acetylsalicylic acid	51	6	13	11	7	5	5

Table 7. Presence or absence of lepra reaction lesions at various sites at initial examination and their evolution after specified periods of treatment

Site of lesion	Treatment (drug)	Lesions present initially		Improved or absent lesions expressed as a percentage of all reactions after specified periods of treatment								
				48 hours			96 hours			8 days		
		Present (%)	Absent (%)	Improved	Absent	Total [a]	Improved	Absent	Total [a]	Improved	Absent	Total [a]
skin	thalidomide	94.8	5.2	62.6	6.1	68.7	48.3	39.7	88.0	14.8	75.4	90.2
	acetylsalicylic acid	95.9	4.1	28.1	6.3	34.4	38.2	11.7	49.9	24.7	25.8	50.5
nerves	thalidomide	70.7	29.3	20.9	35.7	56.6	14.7	50.0	64.7	7.8	58.3	66.1
	acetylsalicylic acid	62.2	37.8	9.4	38.6	48.0	7.4	47.9	55.3	6.4	50.0	56.4
eyes	thalidomide	16.4	83.6	4.3	86.1	90.4	1.7	89.7	91.4	1.7	89.6	91.3
	acetylsalicylic acid	17.3	82.7	3.1	86.5	89.6	3.2	86.2	89.4	2.1	87.2	89.3
testes	thalidomide	21.6	78.4	7.8	82.6	90.4	4.3	87.9	92.2	3.5	91.3	94.8
	acetylsalicylic acid	17.3	82.7	3.1	82.3	85.4	1.1	87.2	88.3	3.2	88.3	91.5
lymphnodes	thalidomide	57.8	42.2	17.4	45.2	62.6	9.5	53.4	62.9	7.8	59.1	66.9
	acetylsalicylic acid	48.0	52.0	5.2	56.3	61.5	10.6	58.5	69.1	7.4	64.9	72.3
liver	thalidomide	27.6	72.4	12.2	74.8	87.0	7.6	82.8	90.4	6.1	85.2	91.3
	acetylsalicylic acid	19.4	80.6	3.1	78.2	81.3	4.3	80.9	85.2	3.2	84.1	87.3
spleen	thalidomide	11.2	88.8	5.2	87.8	93.0	2.6	91.4	94.0	2.6	92.2	94.8
	acetylsalicylic acid	11.2	88.8	2.1	86.5	88.6	1.1	87.2	88.3	3.2	89.4	92.6

[a] Total = improved + absent.

48 hours, 96 hours, and 8 days were 69%, 88%, and 90%, respectively. The corresponding proportions in the acetylsalicylic acid group were 34%, 50%, and 51%. Thus either treatment is attended by a regression of the skin lesions, but the regression following thalidomide treatment was almost double that with acetylsalicylic acid treatment

Initially, 29.3% of the reactions treated by thalidomide and 37.8% by acetylsalicylic acid were free from nerve lesions. After 48 hours, 96 hours, and 8 days, the proportions free from such lesions, or in a state of improvement, were 57%, 65%, and 66%, respectively, in the thalidomide group. In the acetylsalicylic acid group the proportions were 48%, 55%, and 56%. Here again, the thalidomide group did better, although the improvements were less dramatic.

The proportions of patients with lesions of the eyes, testes, lymph nodes, liver, and spleen were smaller in both groups, even initially. Even so, both drugs seem to have conferred some benefit to those with lesions, the effect of thalidomide treatment being consistently superior.

Blood pressure (Table 8)

It will be observed that initially 24 cases in the thalidomide group and 20 cases in the acetylsalicylic acid group (all of whom were adults) had a diastolic blood pressure of 30–50 mm Hg and that subsequently, the fall of diastolic blood pressure was slightly more in the thalidomide group than in the acetylsalicylic acid group. With regard to the systolic blood pressure, 20 cases in the thalidomide

Table 8. Initial and subsequent blood pressure (separately for systolic and diastolic) in reactions treated with thalidomide or acetylsalicylic acid

mm Hg	Thalidomide				Acetylsalicylic acid			
	Initial	48 hours	96 hours	8th day	Initial	48 hours	96 hours	8th day
				Diastolic pressure				
30	2	2	1	0	2	0	2	3
40	5	13	7	9	4	8	4	4
50	17	15	22	16	14	13	15	14
60	31	32	37	37	27	35	35	29
70	38	35	33	31	26	21	20	28
80	21	18	16	21	23	18	18	14
90	2	0	0	0	2	2	1	1
no information	0	1	0	2	0	1	3	5
				Systolic pressure				
60	1	0	0	0	2	0	0	2
70	3	3	2	1	0	0	1	1
80	3	10	12	10	3	4	7	5
90	15	20	17	23	18	24	19	18
100	31	29	27	26	26	20	25	24
110	22	22	27	24	17	23	18	18
120	21	22	22	22	21	19	14	17
130	14	5	6	6	8	2	7	7
140	4	2	2	2	2	4	2	1
150	0	1	0	0	1	0	1	0
160	2	1	1	0	0	1	1	0
no information	0	1	0	2	0	1	3	5

Table 9. Initial and subsequent pulse rate in lepra reactions treated with thalidomide and acetylsalicylic acid

Pulse rate/min	No. of reactions							
	Thalidomide				Acetylsalicylic acid			
	Initial	48 hours	96 hours	8th day	Initial	48 hours	96 hours	8th day
50	—	2	8	8	2	—	2	2
60	5	10	21	34	3	5	7	7
70	24	38	45	42	22	22	24	30
80	28	40	33	22	27	30	25	21
90	15	11	4	2	17	18	11	12
100	23	7	1	1	20	14	19	13
110	8	2	—	—	3	4	5	4
120	6	1	—	—	4	4	2	2
130	2	—	—	—	—	—	—	—
no information	5	5	4	7	0	1	3	7
Total	116	116	116	116	98	98	98	98

group and 11 in the acetylsalicylic acid group had 130 mm Hg and over; on the eighth day there were 8 cases in each group with 130 mm Hg and over. Therefore, the fall in the systolic pressure to apparently normal values occurred more often with thalidomide.

Pulse rate (Table 9)

It will be observed that initially, in the thalidomide group, there was not even 1 case with a pulse rate below 60/min, but on the eighth day there were 8 cases with this pulse rate. A similar observation was not made in the acetylsalicylic acid group. There was a tendency to bradycardia in the thalidomide group and this is probably related to the sedative action of the drug and also to the decrease of temperature, more evident and striking with this drug than with acetylsalicylic acid.

LABORATORY EXAMINATIONS

White blood cell counts (Table 10)

In about 50% of reactions treated with thalidomide or acetylsalicylic acid, leucocytosis (more than 11 000 white cells per mm^3) was observed at the initial

Table 10. Initial and subsequent total white blood cell counts in reactions treated with thalidomide or acetylsalicylic acid

Examination	Treatmnte	White blood cell total counts/mm^3				
		$< 4 \times 10^3$	$4–11 \times 10^3$	$> 11 \times 10^3$	no information	Total
nitial	thalidomide	2	44	53	17	116
	acetylsalicylic acid	0	44	41	13	98
subsequent to 8th day	thalidomide	4	82	25	5	116
	acetylsalicylic acid	0	46	44	8	98

examination. By the eighth day it had normalized in 50% in the thalidomide group, while remaining unchanged in the acetylsalicylic acid group. On the other hand, leucopaenia was observed in 2 reactions before treatment with thalidomide and, at the end, in 4 reactions. There was a tendency for a fall of the total white cell count in the thalidomide group. Admittedly, when lepra reaction subsides, there is a tendency for the white cell count to fall, and this may be responsible for the fall in the count of patients treated with thalidomide and in whom better results were obtained. The other possibility is that the drug itself may induce leucopaenia.

White blood cell differential counts (Table 11)

Information is available for only 53 reactions treated with thalidomide and 39 treated with acetylsalicylic acid at initial examination, and for 55 and 42 reactions, respectively, in subsequent (eighth day) examination. The most important aspect to be considered here concerns the neutrophils.

Neutrophilia was observed at the initial examination in 53% of reactions in the thalidomide group and 49% in the group of reactions treated with acetylsalicylic acid. After 7 days of treatment, neutrophilia was present in 9% of reactions in the thalidomide group and in 40% in the acetylsalicylic

Table 11. Initial and subsequent differential white cell counts in reactions treated with thalidomide or acetylsalicylic acid

White blood cells	Differential counts (%)	Initial examination		Subsequent examination	
		Thalidomide	Acetylsalicylic acid	Thalidomide	Acetylsalicylic acid
neutrophils	< 50	1	1	16	2
	50–74	24	19	34	23
	⩾ 75	28	19	5	17
	no information	63	59	61	56
ymphocytes	< 20	39	23	13	26
	20–44	14	16	42	16
	⩾ 45 %	0	0	0	0
	no information	63	59	61	56
monocytes	< 2	24	14	5	14
	2–9	21	19	29	16
	⩾ 10	7	3	21	12
	no information	64	62	61	56
eosinophils	0	4	2	1	3
	1–6	47	36	53	38
	6	0	0	0	0
	no information	65	60	62	57
basophils	0	0	0	1	1
	1–2	2	1	0	2
	3	0	0	0	0
	no information	114	97	115	95

Table 12. Initial and subsequent red blood cell counts in reactions treated with thalidomide or acetylsalicylic acid

Examination	Treatment	Red blood cell counts/mm³				
		$< 4 \times 10^6$	$4.0–4.9 \times 10^6$	$5.0–5.9 \times 10^6$	$\geqslant 6.0 \times 10^6$	No information
initial	thalidomide	57	12	1	0	46
	acetylsalicylic acid	44	16	0	0	38
subsequent	thalidomide	61	17	4	0	34
	acetylsalicylic acid	55	10	2	0	31

acid group. On the other hand, neutropaenia was present in 29% of reactions after 8 days' treatment with thalidomide but in only 5% in the acetylsalicylic acid group (could this be due to a side effect?).

Red blood cell counts (Table 12)

Red blood cell counts were below normal (4×10^6) in 81% of reactions in the thalidomide group and in 73% of the acetylsalicylic acid group at the initial examination. No significant difference was observed after 7 days' treatment in both groups. It is rather difficult to assess the real significance of this anaemia since this condition is common in tropical countries (malaria, parasitosis, etc.).

Urine analysis (Table 13)

Albumin was present in 20% of reactions treated with thalidomide and 23% in reactions treated with acetylsalicylic acid at initial examinations. After 7 days' treatment, albumin was present in 7% and 16%, respectively.

Table 13. Presence or absence of albumin, sugar, urobilinogen, and bile pigments in urine at initial and subsequent examination in lepra reactions treated with thalidomide or acetylsalicylic acid

Urine analysis		Initial examination		Subsequent examination	
		Thalidomide	Acetylsalicylic acid	Thalidomide	Acetylsalicylic acid
albumin	present	20	20	7	13
	absent	78	66	91	68
	no information	18	12	18	17
sugar	present	0	0	0	0
	absent	70	61	70	57
	no information	46	37	46	41
urobilinogen	present	5	2	0	1
	absent	18	21	23	20
	no information	93	75	93	77
bile pigments	present	2	2	1	1
	absent	21	21	22	20
	no information	93	75	93	77

Table 14. Initial and subsequent erythrocyte sedimentation rates in reactions treated with thalidomide or acetylsalicylic acid

Examination	Treatment	Hour	Sedimentation rates (mm/hour)						
			< 3	3–4	5–9	10–19	20–29	⩾ 30	No information
initial	thalidomide	1st	0	1	1	1	6	87	20
		2nd	0	0	0	2	2	83	29
	acetylsalicylic acid	1st	1	2	0	0	10	71	14
		2nd	0	0	1	2	0	74	21
subsequent	thalidomide	1st	0	0	1	7	6	94	8
		2nd	0	0	0	1	3	85	27
	acetylsalicylic acid	1st	0	0	0	3	10	76	9
		2nd	0	0	0	0	3	71	24

Table 15. Initial and subsequent blood urea nitrogen levels in reactions treated with thalidomide or acetylsalicylic acid

Examination	Treatment	Blood urea nitrogen levels (mg/100 ml)				
		< 20	20–29	30–49	⩾ 50	No information
initial	thalidomide	25	28	43	2	18
	acetylsalicylic acid	16	24	40	4	14
subsequent	thalidomide	24	46	37	3	6
	acetylsalicylic acid	22	22	43	2	9

Sugar was absent in all reactions of both groups, before and after treatment.

Information on urobilinogen and bile pigments is incomplete.

Erythrocyte sedimentation rate (Table 14)

Sedimentation rates are in general high (⩾30 mm/hour) in all reactions, irrespective of whether they were treated with thalidomide or acetylsalicylic acid. No modification was observed after 7 days' treatment.

Blood urea nitrogen levels (Table 15)

Thalidomide and acetylsalicylic acid groups of reaction were similar for blood urea nitrogen levels. After 7 days' treatment, no substantial differences were found in either group.

Aminotransferase levels (SGOT, SGPT) [1] (Tables 16 and 17)

From the information available, it seems that aminotransferase levels in lepra reactions have not been influenced by treatment with thalidomide or acetylsalicylic acid. In the majority of reactions in either group, aminotransferase levels could be considered normal.

[1] SGPT = L-alanine: 2-oxoglutarate aminotransferase (2.6.1.2).

Table 16. Initial and subsequent aminotransferase levels (SGOT) in lepra reactions treated with thalidomide or acetylsalicylic acid

Examination	Treatment	Aminotransferase levels (SGOT) (B units)					
		< 30	30–39	40–49	50–59	⩾ 60	No information
nitial	thalidomide	58	7	7	3	1	40
	acetylsalicylic acid	46	9	2	1	4	36
subsequent	thalidomide	57	17	2	1	3	36
	acetylsalicylic acid	47	8	5	0	3	35

Table 17. Initial and subsequent aminotransferase levels (SGPT) in lepra reactions treated with thalidomide and acetylsalicylic acid

Examination	Treatment	Aminotransferase levels (SGPT) (F units)					
		< 40	40–49	50–59	60–69	⩾ 70	No information
initial	thalidomide	71	5	0	0	2	38
	acetylsalicylic acid	59	0	0	1	2	36
subsequent	thalidomide	74	1	4	1	2	34
	acetylsalicylic acid	60	1	0	0	2	35

Side effects (Table 18)

The majority of symptoms considered in the table as possible side effects were observed indistinctly in both the thalidomide and acetylsalicylic acid groups, with no significant difference. It is most likely, therefore, that they were not really side effects due to treatment but rather symptoms of the lepra reaction.

The only symptom listed that could be considered as a side effect due to thalidomide is leucopaenia, which was observed in 14% of the reactions treated with this drug but in only 2% of those treated with acetylsalicylic acid. Dryness and vomiting seem to have occurred more often with acetylsalicylic acid.

From data available, difficulty of erection was observed in the same number of cases treated by thalidomide and acetylsalicylic acid.

DISCUSSION

The results obtained in this short-term trial confirm the reports on the effects of thalidomide in certain symptoms of lepra reaction. The drug had a striking effect on the body temperature. When lepra reactions were treated with thalidomide, skin lesions had disappeared in about 73% of the reactions by the eighth day, while this happened with acetylsalicylic acid in about 23%; furthermore, in about 52% of the reactions, the skin lesions remained unchanged in the acetylsalicylic acid group. Thalidomide also seemed to give better results than acetylsalicylic acid in acute nerve lesions. Nevertheless, comparing thalidomide activity on nerve and skin lesions, it appeared that the drug is more effective on the latter; in fact, in about 48% of the reactions, the neuritis apparently continued unchanged at the seventh day of treatment. Lesions in the eyes, like the nerve lesions, did not appear to respond as well as the skin lesions. Lesions of testes, lymph nodes, liver, and spleen related to lepra reactions, responded more quickly and intensively with thalidomide than with acetylsalicylic acid. From the double-blind trial, it also appeared that acetylsalicylic acid was helpful in the management of lepra reactions, although its action was definitely inferior to that of thalidomide.

Table 18. Side effect observed in lepra reactions treated with thalidomide or acetylsalicylic acid

Side-effects	Treatment[a]	Present	Absent	No information
drowsiness	Th.	6	58	52
	Ac.	4	52	42
urticaria	Th.	1	63	52
	Ac.	0	56	42
skin rash	Th.	4	60	52
	Ac.	4	52	42
dryness	Th.	12	52	52
	Ac.	17	39	42
oedema	Th.	5	59	52
	Ac	5	51	42
headache	Th.	12	52	52
	Ac.	11	45	42
nausea	Th.	4	60	52
	Ac.	7	49	42
numbness	Th.	1	63	52
	Ac.	0	56	42
itching	Th.	2	62	52
	Ac.	2	54	42
paraesthesia	Th.	3	61	52
	Ac.	6	50	42
constipation	Th.	7	57	52
	Ac.	3	53	42
dizziness		16	48	52
	Ac.	14	42	42
eucopaenia	Th.	9	55	52
	Ac.	1	55	42
vomiting	Th.	1	63	52
	Ac.	6	50	42

[a] Th = thalidomide; Ac = acetylsalicylic acid.

With regard to laboratory examinations, a tendency to leucopaenia was noticed in the thalidomide group; the drug could have induced it but a fall of the total white cells has been reported when a lepra reaction subsides. Nevertheless, the possibility of leucopaenia, and also of neutropaenia, developing with prolonged use of thalidomide should be seriously considered. Erythrocyte sedimentation rates did not appear to have been influenced either by thalidomide or by acetylsalicylic acid at the end of 7 days' treatment.

Concerning side effects, thalidomide is known to cause 3 types of severe adverse reactions: teratogenic effects (various types of malformation, mainly dysmelia), leucopaenia, and peripheral neuritis. Teratogenic effects have been observed after a single dose of 200 mg of thalidomide administered on the fortieth day of pregnancy. Leucopaenia occurred early or later in leprosy patients during thalidomide treatment. Peripheral neuritis has been observed occasionally; this type of adverse reaction may lead to permanent nerve damage. The early detection and differential diagnosis of drug-induced neuritis has its specific difficulties in leprosy patients because of the neuritis caused by *Mycobacterium leprae*. Thalidomide therapy is, therefore, attended by high risks.

In the present short-term trial, carried out with male patients only in which thalidomide was administered for very short periods (7 days or a maximum of 2 weeks), the majority of symptoms that could be attributed to possible side effects were observed indistinctly with both thalidomide and acetylsalicylic acid treatment, and possibly they were caused by the lepra reaction. From data available, difficulty of erection was reported in both trial groups in the same number of cases. As indicated above, it seems that thalidomide has a tendency to induce leucopaenia. The influence of thalidomide on the blood pressure and pulse rate is worth noting. It seems that the striking bradycardia in patients of the thalidomide group cannot be attributed entirely to the fall of body temperature. In some instances, irregularities of cardiac rhythm were observed.

CONCLUSIONS

(1) Thalidomide seems to bring about reduction of skin lesions, and a fall in body temperature in a larger number of cases and in a shorter period than acetylsalicylic acid does;

(2) The effect of thalidomide on acute nerve and eye lesions seems to be less pronounced, though more satisfactory than that of acetylsalicylic acid;

(3) Both drugs seem to have conferred some benefit on patients with involvement of testes, lymph nodes, liver, and spleen, related to lepra reactions; the effect of thalidomide treatment is consistently superior;

(4) It appears that acetylsalicylic acid is helpful in the management of certain symptoms of the lepra reaction;

(5) In the very short period of treatment, side effects of a serious nature have not been encountered in either group. Thalidomide appears to have a tendency to induce leucopaenia and probably a fall in the pulse rate.

RÉSUMÉ

ESSAI À COURT TERME ET À DOUBLE INSU, COORDONNÉ PAR L'OMS, DE LA THALIDOMIDE DANS LE TRAITEMENT DES RÉACTIONS LÉPREUSES AIGUËS CHEZ DES MALADES LÉPROMATEUX DE SEXE MASCULIN

En 1967, l'OMS a organisé un essai à double insu, d'une durée de 9 mois environ, afin d'évaluer l'efficacité de la thalidomide dans le traitement de la réaction lépreuse. Quatre centres de recherche en Espagne, en Inde, au Mali et en Somalie ont participé à ces investigations qui ont porté sur 92 malades.

Au cours de l'essai, on a enregistré 214 réactions lépreuses; 116 d'entre elles ont été traitées par la thalidomide et 98 par l'acide acétylsalicylique. Dans chaque cas, le traitement a duré 7 jours. D'après une étude statistique préalable, il était prévu de traiter quatre épisodes réactionnels chez chaque malade, dont deux par la thalidomide et deux par l'acide acétylsalicylique. Cet objectif n'a pas été atteint parce que certains malades traités par la thalidomide n'ont plus présenté par la suite de réactions qui, si elles s'étaient produites, auraient été traitées par l'acide acétylsalicylique.

Les observations faites amènent les auteurs à formuler un certain nombre de conclusions:

a) il semble que la thalidomide entraîne une amélioration des lésions cutanées et une chute de la température dans une proportion plus élevée des cas et dans un délai plus bref que l'acide acétylsalicylique;

b) l'action de la thalidomide sur les lésions nerveuses et oculaires aiguës est moins marquée, mais elle est cependant plus nette que celle de l'acide acétylsalicylique;

c) les deux médicaments semblent agir favorablement sur les atteintes testiculaires, ganglionnaires, hépatiques et spléniques accompagnant la réaction lépreuse; la thalidomide fait cependant preuve d'une efficacité supérieure;

d) le traitement par l'acide acétylsalicylique permettrait d'atténuer certains symptômes de la réaction lépreuse;

e) durant les brèves périodes de traitement (7 jours), on n'a relevé aucun effet secondaire grave dans les deux groupes de malades. La thalidomide pourrait provoquer un certain degré de leucopénie et une diminution de la fréquence du pouls.

Il paraît donc prouvé que l'on peut retirer des avantages cliniques certains de l'emploi de la thalidomide pour le traitement des réactions lépreuses. Il importe cependant de ne pas perdre de vue les effets adverses graves, par ailleurs bien connus, qui peuvent résulter de l'usage de ce médicament.

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