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Adverse events of standardized regimens of corticosteroids for prophylaxis and treatment of nerve function impairment in leprosy: results from the 'TRIPOD' trials

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Summary Reactions in leprosy causing nerve function impairment (NFI) are increasingly treated with standardized regimens of corticosteroids, often under field conditions. Safety concerns led to an assessment of adverse events of corticosteroids, based on data of three trials studying prevention of NFI (the TRIPOD study). A multicentre, randomized, double-blind placebo-controlled trial was conducted in leprosy control programmes in Nepal and Bangladesh. Treatment was with prednisolone according to fixed schedules for 16 weeks, starting in one trial with 20 mg/day (prophylactic regimen: total dosage 1·96 g) and in the other two trials with 40 mg/day (therapeutic regimen: total dosage 2·52 g). Minor adverse events were defined as moon face, fungal infections, acne, and gastric pain requiring antacid. Major adverse events were defined as psychosis, peptic ulcer, glaucoma, cataract, diabetes and hypertension. Also, the occurrence of infected plantar, palmar, and corneal ulceration was monitored, together with occurrence of TB. Considering all three trials together, minor adverse events were observed in 130/815 patients (16%). Of these, 51/414 (12%) were in the placebo group and 79/401 (20%) in the

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prednisolone group. The relative risk for minor adverse events in the prednisolone group was 1·6 ($P = 0{\cdot}004$). Adverse events with a significantly increased risk were acne, fungal infections and gastric pain. Major adverse events were observed in 15/815 patients (2%); 7/414 (2%) in the placebo group and 8/401 (2%) in the prednisolone group. No major adverse events had a significantly increased risk in the prednisolone arm of the trials. No cases of TB were observed in 300 patients who could be followed-up for 24 months. Standardized regimens of corticosteroids for both prophylaxis and treatment of reactions and NFI in leprosy under field conditions in developing countries are safe when a standard pre-treatment examination is performed, treatment for minor conditions can be carried out by field staff, referral for specialized medical care is possible, and sufficient follow-up is done during and after treatment.

Introduction

Reactions in leprosy patients causing acute nerve function impairment (NFI) can often be treated successfully with corticosteroids. Treatment with corticosteroids in leprosy control programmes is increasingly being provided under field conditions, often by paramedical workers. For this reason, standardized regimens have been adopted. Courses of 12 weeks for paucibacillary (PB) patients and 20 weeks for multibacillary (MB) patients have been recommended,[1] but different time schedules are also possible.[2] The initial dose is usually 40 mg daily, which is tapered off over the treatment period. General introduction of standard regimens in leprosy control programmes has been hesitant, primarily for fear of the complications of corticosteroids. There is uncertainty about the frequency of occurrence of adverse events, and anxiety that paramedical staff might overlook them. The risks of standardized regimens of corticosteroids for the treatment of leprosy reactions in the field have been described previously.[3] This information, however, was primarily based on knowledge of adverse events of corticosteroids as found in trials conducted in developed countries. A systematic evaluation of the use of corticosteroids under field conditions in developing countries has never been performed.

Concerns about safety led to an assessment of adverse events of corticosteroids based on data from the three recent field trials studying prevention of NFI (Trials in Prevention of Disability: TRIPOD). These trials were conducted in Nepal and Bangladesh with the aim to study the prevention of NFI in leprosy by means of corticosteroids. TRIPOD was a multicentre, randomized, double-blind placebo-controlled trial. Two different standard regimens were tested, both with a duration of 16 weeks. The first regimen started with a daily dose of 20 mg prednisolone (prophylactic regimen), the other regimen started with a daily dose of 40 mg (therapeutic regimen). The results of the TRIPOD trials are described elsewhere.[4–6] This paper reports on adverse events of prednisolone in the three separate trials.

Materials and methods

STUDY POPULATION

The trial was conducted in six leprosy control programmes in Nepal and Bangladesh. In Nepal the control programmes were in Dhanusha District in the Central Region, Morang District in the Eastern Region and in the Terai Districts of the Western Region. The Leprosy Division of the Ministry of Health of His Majesty's Government, Nepal, runs

these programmes with technical assistance from the Nepal Leprosy Trust, Netherlands Leprosy Relief and the International Nepal Fellowship, respectively. In Bangladesh the control programmes were in North-West Bangladesh, Dhaka and Chittagong, run by The Leprosy Mission (TLM), in co-operation with the Government of Bangladesh.

STUDY DESIGN

The main objective of the TRIPOD was to study the prevention and treatment of nerve function impairment (NFI) in leprosy by means of corticosteroids. The study design was that of a multicentre, randomized, double-blind placebo-controlled trial. Patients were randomized to either of the two arms of the trial using a randomization within each leprosy control programme. One treatment group received a standardized prednisolone regimen, the other a placebo regimen. Treatment prescribers, study coordinators, and patients were unaware who was in the treatment and placebo group.

The first trial (TRIPOD 1), investigated whether treatment with low dose (20 mg/day) prednisolone for the first 4 months of the MDT treatment period resulted in a reduction in the number of patients experiencing one or more episodes of type 1 (reversal) reaction leading to NFI, in patients with multibacillary leprosy at diagnosis, compared to those who received placebo treatment for the same period. Patients receiving prednisolone started with a dose of 20 mg/day for 3 months and then a tapering dose of 15 mg/day for 1 week, 10 mg/day for 2 weeks, and finally 5 mg/day for 1 week. Patients receiving placebo took an equivalent number of identical placebo tablets for the same time period. The placebo tablets were prepared by the same company as the prednisolone tablets used in the trials. The second trial (TRIPOD 2) investigated whether patients who tested normal on the ball pen test, but who were diagnosed to have mild sensory function impairment with the Semmes-Weinstein monofilament test, had a better outcome than similarly impaired patients who received placebo treatment. Patients receiving prednisolone started with a dose of 40 mg/day. The dose was tapered by 5 mg/day every 2 weeks and was completed after 16 weeks. Patients receiving placebo took an equivalent number of identical placebo tablets for the same time period. The third trial (TRIPOD 3) investigated whether patients who had untreated NFI which commenced between 6 and 24 months previously and were given standard steroid therapy, had a better treatment outcome than similarly impaired patients who received placebo treatment. As with TRIPOD 2, patients receiving prednisolone started with a dose of 40 mg/day. The dose was tapered by 5 mg/day every 2 weeks and was completed after 16 weeks. Patients receiving placebo took an equivalent number of identical placebo tablets for the same time period. Ethical clearance was received for all three trials.

For all trials, leprosy patients aged from 15 to 60 years, and on treatment with WHO MB multidrug therapy (MDT), were eligible if they had a positive skin smear or six or more skin lesions at diagnosis. Additional inclusion criteria were formulated for each separate trial.[4–6] Excluded from the trials were any patients for whom corticosteroids would be indicated at study registration because of leprosy reactions, other evidence of acute NFI, or any other medical indication requiring steroids. Also patients were excluded if NFI of the eligible nerve had been treated surgically. Finally, patients for whom corticosteroids at the fixed trial dose would be contraindicated, were also excluded from the study. These contraindications were as follows:

- Bodyweight less than 35 kg.
- Presence of peptic ulcer, or history suggesting peptic ulcer, haematemesis or melaena, or gastric pain sufficient to disturb sleep.

- History of psychosis or endogenous depression.
- Presence of acute or chronic bacterial infection, including tuberculosis and infected neuropathic ulcers.
- Presence of corneal ulceration or mature cataract.
- History of glaucoma.
- History of diabetes mellitus or a measured urine sugar level > 2+.
- History of hypertension or a measured diastolic blood pressure of > 100 mmHg.
- Use of anti-epileptic and antihypertensive medication, and oral contraceptives.
- Pregnancy at entry into the trial.

All patients also received albendazole prophylaxis for helminth infections at the entry of the trial. They were requested to attend monthly follow-up clinics for assessment while taking treatment. An outcome assessment was done at completion of treatment at 4 months, and at 6, 9, and 12 months after the start of treatment. The trial commenced on 1 April 1998, and intake of patients took until 30 June 2000.

OUTCOMES REGARDING ADVERSE EVENTS ASSOCIATED WITH STEROIDS

During follow-up, all patients were examined for the presence of adverse events associated with prednisolone. Minor adverse events were defined in advance and specifically asked for, namely moon face, fungal infections, acne, and gastric pain requiring antacid. These events were recorded during the first 4 months of the trial only. Patients exhibiting signs of these conditions were treated appropriately, but remained in the trial unless the patient requested it. Major adverse events were defined as psychosis, peptic ulcer, glaucoma, cataract, diabetes and hypertension. These events were checked throughout the trial. Patients exhibiting these signs and symptoms were treated appropriately, but discontinued participation in the trial. Another important reason to discontinue participation in the trial was any event leading to the prescription of prednisolone. Such events were known as 'steroid-triggering events' and included type 1 (RR) or type 2 (ENL) leprosy reactions and any signs of recent NFI.

STATISTICAL ANALYSIS

Statistical analysis was done in EPI INFO version 6.04. Risk ratios (RR) and 95% confidence intervals were calculated.

Results

A total of 815 patients were recruited into the three TRIPOD trials, of which 414 were randomly allocated to the placebo arms and 401 to the prednisolone arms. Of the total, 475 came from Bangladesh and 340 from Nepal (Table 1). The number of patients with minor adverse events was 110 (23%) in Bangladesh and 20 (6%) in Nepal. The RR of being diagnosed with minor adverse events given that the patient is from Bangladesh is 3·94 (95% CI: 2·50–2·61). This difference in the proportion of patients diagnosed with minor adverse events is statistically significant at centre level as well. The RR of experiencing minor adverse events given that the patient is in the prednisolone arm is 1·49 (95% CI: 1·06–2·08; $P = 0{\cdot}02$) for Bangladesh, and 2·42 (95% CI: 0·95–6·14; $P = 0{\cdot}09$) for Nepal. The overall RR is 1·60 (95% CI: 1·16–2·21), which is statistically significant ($P = 0{\cdot}004$).

Table 1. Total number of patients with minor adverse events in the TRIPOD trials, according to country and treatment group

	Placebo			Prednisolone			Statistical significance		
Country	PaR[a]	PwA[b]	%	PaR[a]	PwA[b]	%	Risk ratio	95% CI	*P*-value
Bangladesh	241	45	19%	234	65	28%	1·49	(1·06–2·08)	0·02
Nepal	173	6	3%	167	14	8%	2·42	(0·95–6·14)	0·09
Total	414	51	12%	401	79	20%	1·60	(1·16–2·21)	0·004

[a] Persons at risk.
[b] Persons with adverse events.

In Table 2, the results are given according to the dosage of prednisolone received. A total of 636 patients received the prophylactic regimen, starting with 20 mg/day (TRIPOD 1). Minor adverse events were seen in 106 patients (17%). The RR of being diagnosed with minor side effects, given that the patient received prednisolone, is 1·71 (95% CI; 1·19–2·46; $P = 0{\cdot}004$). There were 179 patients included in the TRIPOD 2 and 3 trials, receiving the therapeutic regimen of prednisolone starting with 40 mg/day. Minor adverse events were observed in 24 patients (13%). The RR of being diagnosed with minor adverse event, given that the patient received prednisolone, is 1·20 (95% CI: 0·57–2·52; $P = 0{\cdot}80$).

Individual adverse events in the prophylactic and therapeutic regimen groups are given in Table 3. In the prophylactic group (20 mg) statistically significant differences ($P < 0{\cdot}05$) between the two arms of the trial can be demonstrated for all adverse events except moon face ($P = 0{\cdot}40$). In the therapeutic group (40 mg), the numbers of individual adverse events are too small to demonstrate statistically significant differences between the two arms of the trial. Gastric pain requiring antacid was the most frequent observed adverse event in all trials together (121/815 or 15%). It was recorded in 12% of the patients in the placebo group and in 18% in the prednisolone group. The difference is statistically significant ($P = 0{\cdot}02$). None of the minor adverse events observed required stopping of treatment and removal from the trials.

Table 4 shows the major adverse events that were recorded during the trials. Major adverse events were observed in 15/815 patients (2%); 7/414 (2%) in the placebo group and 8/401 (2%) in the prednisolone group. No major adverse events had a significantly increased

Table 2. Total number of patients with minor adverse events in the TRIPOD trials, according to regimen and treatment group

	Placebo			Prednisolone			Statistical significance		
Starting dosage	PaR[a]	PwA[b]	%	PaR[a]	PwA[b]	%	Risk ratio	95% CI	*P*-value
20 mg/day	324	40	12%	312	66	21%	1·71	(1·19–2·46)	0·004
40 mg/day	90	11	12%	89	13	15%	1·20	(0·57–2·52)	0·80
Total	414	51	12%	401	79	20%	1·60	(1·16–2·21)	0·004

[a] Persons at risk.
[b] Persons with adverse events.

Table 3. Minor adverse events in the prophylactic regimen group (starting with a daily dosage of 20 mg prednisolone), the therapeutic regimen group (starting with a daily dosage of 40 mg prednisolone), and both groups taken together

Adverse event	Placebo			Prednisolone			Statistical significance		
	PaR[a]	PwA[b]	%	PaR[a]	PwA[b]	%	Risk ratio	95% CI	*P*-value
20 mg/day									
Moon face	324	6	2%	312	10	3%	1·78	(0·64–4·71)	0·40
Acne	324	1	0·3%	312	9	3%	9·35	(1·19–73·34)	0·02
Fungal infection	324	0	–	312	5	2%	–	–	0·03
Gastric pain	324	39	12%	312	60	14%	1·60	(1·10–2·32)	0·02
40 mg/day									
Moon face	90	3	3%	89	2	2%	0·67	(0·12–3·94)	0·99
Acne	90	2	2%	89	0	–	–	–	>0·05
Fungal infection	90	0	–	89	0	–	–	–	–
Gastric pain	90	10	11%	89	12	13%	1·21	(1·53–2·66)	0·80
Together									
Moon face	414	9	2%	401	12	3%	1·38	(0·59–3·23)	0·66
Acne	414	3	0·7%	401	9	2%	3·10	(0·84–11·36)	0·13
Fungal infection	414	0	–	401	5	1%	–	–	0·07
Gastric pain	414	49	12%	401	72	18%	1·52	(1·08–2·12)	0·02

[a] Persons at risk.
[b] Persons with adverse events.

risk in the prednisolone arm of the trials. No cases of tuberculosis were observed in 300 patients who were followed-up for 24 months. In addition to the above major adverse events that led to removal from the trial, there were three deaths during the trials. All three patients were taking placebo. One patient died at 2 months after registration in the trial, another at 7 months after registration. The cause of death is unknown of both cases. A third patient died just before the 24-month follow up due to encephalitis.

Table 4. Major adverse events in the prophylactic and therapeutic regimen groups taken together

Adverse event	Placebo			Prednisolone			Statistical significance		
	PaR[a]	PwA[b]	%	PaR[a]	PwA[b]	%	Risk ratio	95% CI	*P*-value
Peptic ulcer	414	1	0·2%	401	2	0·5%	2·06	(0·19–22·68)	0·62
Diabetes	414	1	0·2%	401	3	0·7%	3·10	(0·32–29·65)	0·37
Psychosis	414	0	–	401	0	–	–	–	–
Glaucoma	414	0	–	401	0	–	–	–	–
Cataract	414	0	–	401	0	–	–	–	–
Hypertension	414	0	–	401	0	–	–	–	–
Infections	414	4	1%	401	2	0·5%	0·52	(0·10–2·80)	0·69
Infected ulcer	414	1	0·2%	401	1	0·2%	1·03	(0·06–16·45)	1·00
Corneal ulcer	414	0	–	401	0	–	–	–	–
Tuberculosis[c]	414	0	–	401	0	–	–	–	–

[a] Persons at risk.
[b] Persons with adverse events.
[c] Follow-up during 24 months of 300 patients.

Discussion

Considering all three trials together, minor adverse events were observed in 16% of all patients; 12% in the placebo group and 20% in the prednisolone group. The relative risk for minor adverse events in the prednisolone group was 1·6 ($P = 0{\cdot}004$). Adverse events with a significantly increased risk were acne, fungal infections and gastric pain. Major adverse events were observed in 2% of all patients without any significant differences between the placebo and prednisolone arm of the trials. The current study does therefore not indicate that these events should be seen as adverse events of steroid treatment in the dosages used.

In a large meta-analysis including 6602 patients receiving corticosteroids in dosages comparable to those used in the TRIPOD trials, the relative frequency of a number of adverse events was compared in the placebo and steroid groups.[7] Dermatological side-effects occurred four times as frequently in the steroid group (10·5%) as in the placebo group (2·6%). In the TRIPOD study, dermatological side-effects (i.e. moon face, acne, and fungal infections) were seen in 2·9% of the placebo group, and 6·5% of the steroid group. The difference was primarily determined by the occurrence of acne. In the meta-analysis, peptic ulcers were reported to develop in 0·3% of patients in the placebo group, and 0·4% in the steroid group, the difference not being statistically significant. The TRIPOD study showed a similar result. Peptic ulcers were reported in one case (0·2%) and two cases (0·5%) in the placebo and steroid groups, respectively. As in the meta-analysis, the difference is also statistically not significant. In the TRIPOD study, patients were also asked about the occurrence of gastric pain during the treatment phase. This appeared to be a common complaint in both groups, but the difference between the placebo (12%) and the steroid (18%) groups is statistically significant. The meta-analysis reported diabetes more frequently in the steroid group (2·6%) than the placebo group (0·3%), and hypertension was noted 4–5 times more frequently in the steroid group (0·9%) than in the placebo group (0·2%). The meta-analysis also showed that psychological side effects occurred two times more frequently in the steroid group (0·5%) than in the placebo group (0·3%). The differences in these last four categories are statistically significant. Bacterial sepsis, osteoporosis and tuberculosis all occurred more frequently in the steroid than in the placebo group, but the differences are not statistically significant. In the TRIPOD study, diabetes was observed in one patient in the placebo group (0·2%) and in three patients in the steroid group (0·7%), the difference not reaching statistical significance. Hypertension and psychological side effects were not observed at all in either group. Infections and infected ulcers were seen in a small number of cases, but with no statistically significant differences between the groups. Also, tuberculosis was not observed in any of the 300 patients who could be followed-up for 24 months.

Of all patients included in the meta-analysis, the mean daily dose of prednisolone was 35 mg (or its equivalent) for the mean duration of 64 days and a mean total dose of 2·2 g. The study is therefore relevant for the use of corticosteroids in the treatment of NFI in leprosy in field conditions. In the TRIPOD study the two different 16-week (112 days) regimens consisted of 1·96 g and 2·52 g, respectively. The frequency of adverse events in the TRIPOD study is very comparable to the meta-analysis. Apart from dermatological side-effects, which are reversible and usually do not require stopping of treatment, other known adverse events are rare. Statistically significant differences in the incidence of some adverse events that were found in the large meta-analysis were not seen in the TRIPOD study, possibly because of the smaller number of patients included or because the absolute risk of these adverse events is much higher in developed countries. A particularly important conclusion is that both studies

fail to provide evidence that peptic ulcers are an adverse event of steroid treatment in the dosages used. Abdominal pain, a possible sign of peptic ulceration, should not be considered a contra-indication when steroid therapy is indicated. In this case aspirin must not be given and treatment with antacids or ranitidine should be provided along with the steroids.

In the TRIPOD study, no differences in adverse events could be found between the prophylactic and therapeutic regimens. This is partially due to the fact that the number of patients included in the therapeutic regimen trials is relatively small (179), affecting the statistical power. It should also be kept in mind that the difference between both regimens was not very large (approximately 25%), and that therefore large differences in the occurrence of adverse events may not be expected. A remarkable finding was that the frequency of adverse events in both arms of the trial was much lower in Nepal than in Bangladesh. This difference was found at all participating centres in both countries. Special attention was given to this observation, even during the trial, but no satisfactory explanation was found. Nepali patients may be less inclined to complain than patients from Bangladesh or healthcare staff in Bangladesh may be more sensitized to recording minor symptoms.

The results from the TRIPOD study confirm that standardized regimens of corticosteroids for both prophylaxis and treatment of reactions and NFI in leprosy can be used safely in the field in developing countries. There are, however, a number of conditions that should be met. These are the availability and strict application of standard treatment guidelines, opportunity to refer if necessary, and sufficient follow-up during and after treatment. Detailed treatment guidelines for the recognition and management of leprosy reactions at local and referral level have been developed recently by the International Federation of Anti-Leprosy Associations (ILEP).[8] The guidelines include a checklist for field workers of relevant signs and symptoms, and a recommendation for referral for specialist care of the following conditions: pregnancy, under 12 years of age, diabetes, eye involvement (pain and redness of the eyes), ulcers or osteomyelitis, tuberculosis, severe depression or psychosis, and a number of leprosy complications (severe type 2 reaction, NFI during treatment, late NFI, and NFI of more than 6 months duration in newly diagnosed patients). For the following conditions the ILEP guidelines recommend that these are treated by the field worker at the same time as corticosteroids are started: worm infestations, diarrhoea with blood and/or mucus, fungal infections, scabies and epigastric pain. Naturally, appropriate medication for these conditions should be available at field level. The TRIPOD study confirms that the ILEP guidelines are both appropriate and effective. Routine measurement of blood pressure does not appear to be necessary, which is in line with the observation that systemic complications of corticosteroids such as hypertension are dose-related and not likely to be caused by the relatively short courses under discussion in this paper.[9] A high cumulative dose of corticosteroids is also shown to be an important risk factor for the development of tuberculosis.[10] Although patients with mature cataract were excluded from the TRIPOD study, this condition is not really a contra-indication to treatment with corticosteroids. Posterior subcapsular cataract is a known complication of corticosteroids, in particular in children,[11] but in the case cataract is already present at the time of treatment with corticosteroids, it can be managed in the usual way and there is no need to refrain from treatment.

With the application of ILEP guidelines on how to recognize and manage leprosy reactions, there should be no hesitation to implement standard steroid regimens for the treatment of leprosy reactions and NFI in field conditions. The benefit of saving peripheral nerves and thus preventing disability usually far outweighs possible adverse events of treatment with corticosteroids.

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