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Leucocytopenia after rifampicin and ofloxacin therapy in leprosy

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Summary New antimycobacterial agents and combined treatment regimens are being introduced for the treatment of leprosy. Ofloxacin is one such broad spectrum antimicrobial agent. In this study rifampicin plus ofloxacin were administered daily for 4 weeks (daily supervised dose). Two patients (and possibly a third patient who refused all investigations) out of 125 patients developed leucocytopenia during the third week of therapy. It was associated with fever, malaise, nausea and loss of appetite. They recovered after cessation of drug treatment. Patients receiving ofloxacin should be monitored for constitutional symptoms suggestive of this complication even though the risk of such complication may be minimal.

Introduction

A large number of leprosy patients have been treated with DDS monotherapy and multidrug therapy (MDT) as recommended by the World Health Organization (WHO). This regimen containing DDS, rifampicin and clofazimine seems to have minimal side-effects. Newer drug regimen[1] containing newer antimycobacterial drugs[2] are being tried for treatment of leprosy. Ofloxacin is one of the antimycobacterial agents that is under investigation as an antileprosy[2–7] drug. When a new drug is employed in treatment, possible adverse reactions need to be monitored carefully. In this paper three case reports of adverse reactions to antileprosy drugs (ofloxacin plus rifampicin) are presented.

At S.L.R. & T. Centre, Karigiri short-term chemotherapy trial in paucibacillary (PB) leprosy was initiated as part of a randomized double-blind multicentre field trial, sponsored by the World Health Organization (WHO). A total of 125 (previously untreated) PB leprosy patients were included in the study, of whom 44% were male and 56% were females. All of them were adults, i.e. age 15 years and above. Of these patients 40·8% were in the age group of 15–30 years, 56% were in 31–45 years and 3·2% were in 46–65 years of age.

Baseline investigations done (for all 125) leprosy patients at inclusion in the trial were as follows:

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Blood: total WBC count, differential WBC count, haemoglobin %.
Blood sugar, urea, liver function tests.
Urine: albumin, sugar & microscopic examination.
Pregnancy test for all women at inclusion in the trial.

All the patients had normal values before commencement of trial regimen. The study group received daily supervised rifampicin 600 mg and ofloxacin 400 mg for 4 weeks; the control group received WHO–MDT (PB) for 6 months.

The daily dose of rifampicin and ofloxacin was administered by experienced field staff (paramedical worker [leprosy] or non-medical supervisor). All the patients were reviewed by a medical officer once a week during the first 4 weeks of therapy. Apart from this, a patient showing any signs and/or symptoms, e.g. itching, fever, headache, drowsiness, abdominal discomfort, etc. was examined by a medical officer. Hence it was possible to monitor for adverse reactions. Two patients (and possibly a third patient who refused all investigations) were suspected to have developed leucocytopenia. The treatment regimen was decoded and all the three patients were found to have received ofloxacin + rifampicin. All three were females.

Case report 1

Patient No. 2186 (female/53 years of age) was diagnosed as having borderline–tuberculoid (BT) leprosy. Baseline investigations were done and a trial regimen was administered. On the fourth day of treatment she had a fever for one day which subsided without any treatment. On

Table 1. Laboratory investigations—Patient No. 2186

	White blood cell (WBC) counts							
		Differential count %						
Date	Total WBC count mm^3	N	E	B	L	M	Hb g%	PCV %
04.03.94	8300	68	6	–	24	2	11·9	–
14.04.94	5600	59	5	–	32	4	–	–
28.04.94	5000	62	5	–	31	2	11·2	–
29.04.94	4000	56	3	–	39	2	–	–
02.05.94	6300	46	4	–	46	4	–	–
23.07.94	6000	69	3	–	28	–	12·1	–
23.11.94	9700	64	4	–	31	1	11·9	–
		(on steroid therapy)						
28.01.95	–	–	–	–	–	–	13·9	35

N, neutrophil; E, eosinophil, B, basophil; L, leucocyte; M, monocyte; PCV, packed-cell volume.
Blood sugar within normal limits.

Liver function tests (LFT)

04.03.94	Albumin–globulin reversal	(39 g/Lt & 40 g/Lt)
28.04.94	Globulin level more than alubmin.	(30 g/Lt & 35 g/Lt)
	Serum Alk. Phosphatase & SGPT	(49·68 & 48 Units/Lt)
	Serum bilirubin	(3·4 μmol/Lt)
	Serum protein (total)	(65 g/Lt)

the 15th day she had a fever for one day associated with malaise. She was hospitalized and routine investigations (Table 1) were done. The peripheral blood picture revealed that the total WBC count had dropped from 8300 per mm^3 to 5600 per mm^3. The trial regimen was suspended. The WBC dropped to 4000 per mm^3 on the 14th day after suspension of trial regimen. Further investigations ruled out enteric fever (using the Widal test), malaria and infectious mononucleosis. The constitutional symptoms disappeared within 3 days. Recovery of cell count was noted on the 17th day after suspension of the trial regimen without any specific therapy.

Bone marrow aspiration smears stained by May-Grunwald Giemsa could only be done 10 months after the leucopenic episode (as the patient was not willing to be hospitalized). The smears showed cellular fragments and normoblastic maturation, eosinophilia (7%), plasmocytosis (6%), and a slight increase in reticulum cells. A liver function test revealed normal levels of serum bilirubin, serum alkaline phosphatase and SGPT. There was a tendency for albumin and globulin reversal (serum protein) which reverted to normal after cessation of therapy.

This patient had (at inclusion in the study) a large, erythematous, infiltrated patch with an ill-defined margin, dry surface and loss of pain and touch sensation. Her right ulnar nerve was found to be thick without nerve tenderness or neurological deficit. On the 15th day, i.e. at detection of leucocytopenia, the patch was an ill-defined, hypopigmented macule. Six months later she had an ulnar neuritis (right) which subsided with steroid therapy without residual neurological deficit.

She again had a tingling sensation in the right hand associated with tenderness over the right ulnar nerve 9 months after the leucopenic episode. Surgical decompression of the right ulnar nerve relieved the symptoms.

During the 16th month after the leucopenic episode the patch showed erythema and there was a tingling sensation in the right hand. The right ulnar nerve remained thick but not tender. She was started on WHO–MDT (PB) regimen and steroid therapy.

At the end of MDT (PB) of 6-months duration the patch had become a hypopigmented macule but the ulnar nerve remained thick with a similar tingling sensation recurring frequently. There was no neurological deficit.

Case report 2

Patient No. 3881 (female/60 years of age) was registered for treatment of BT leprosy. Routine investigations prior to treatment were found to be within normal limits. She had sleeplessness associated with headaches and excessive salivation during the first few days of treatment. During the third week, i.e. 19th day she developed a fever lasting for one day only, and nausea and loss of appetite lasting for 5 days (including 2 days after suspension of the trial regimen). Examination of systems revealed no abnormalities. Routine investigations revealed that there was leucocytopenia. The total WBC count (Table 2) dropped to 2000 per mm^3 from 10,000 per mm^3. The trial regimen was suspended and the patient was hospitalized. Further investigations ruled out malaria and enteric fever (using the Widal blood test). Recovery of WBC count was noted on the 7th day after suspension of the trial regimen without any specific therapy. The bone marrow aspiration smears of this patient could be done only 11 months after the episode of leucopenia. It showed mild megaloblastic changes and eosinophilia (12%) (recovering marrow except for hypocellularity). A liver function test (LFT) revealed normal levels of serum bilirubin, serum alkaline phosphatase and SGPT. But

Table 2. Laboratory investigations—Patient No. 3881

	White blood cell (WBC) counts							
		Differential count %						
Date	Total WBC count mm^3	N	E	B	L	M	Hb g%	PCV %
23.10.93	10 000	81	4	–	14	1	12·8	40
02.01.94	2 000	56	11	–	33	–	11·9	–
03.01.94	1 600	44	8	–	36	12	–	–
10.01.94	4 900	40	31	1	27	1	11·6	–
17.01.94	8 700	54	29	–	16	1	11·6	–
26.10.94	9 200	38	40	–	21	1	11·6	–
22.11.94	10 800	73	14	–	10	3	11·9	–

See Table 1 for notation.

Liver function tests (LFT)

23.10.93	Albumin : globulin equal	(45 g/L & 45 g/L)
28.04.94	Globulin more than albumin	(30 g/L & 36 g/L)
22.11.94	Albumin : globulin normal	(42 g/L & 36 g/L)
	Serum alk. phosphatase & SGPT	(43·2 & 14 Units/L)
	Serum bilirubin	(3·4 μmol/L)
	Total proteins	(66 g/L)
	Glucose	(6·9375 μmol/L)

there was a tendency for albumin and globulin reversal (serum protein). These changes reverted to normal after cessation of therapy.

She had three erythematous infiltrated patches with partly ill-defined margins on the right arm without involvement of the peripheral nerves. At the time of the leucopenic episode the lesions were regressing though active. One month later the lesions became vague hypopigmented macules (inactive). As there was no signs of disease activity she had been on surveillance without antileprosy chemotherapy.

Case report 3

Patient No. 2185 (female of 30 years age) was started on the trial regimen for BT leprosy

Table 3. Laboratory investigations—Patient No. 2185

	White blood cell (WBC) counts							
		Differential count %						
Date	Total WBC count mm^3	N	E	B	L	M	Hb g%	PCV %
07.03.94	10 600	63	13	1	18	5	13·6	–

See Table 1 for notation.

Liver function tests (LFT)

07.03.94	Albumin : globulin equal	(38 g/L & 34 g/L)
	Serum alk. phosphatase & SGPT levels normal.	
	Serum bilirubin level normal.	

patch on left arm. Results of baseline investigations were within normal limits (Table 3). She had a bitter taste and nausea on the 3rd day of treatment. She was persuaded to continue treatment. The bitter taste persisted associated with loss of appetite and severe abdominal discomfort. It was so disturbing that she refused to continue the treatment on the 19th day. She even refused to undergo investigations. Hence follow-up investigations could not be done. No abnormality was detected on clinical examination. All the symptoms disappeared after termination of therapy. These symptoms were suggestive of drug-induced side-effects similar to the other two patients.

She had three small erythematous infiltrated patches with ill-defined margins and loss of pain and touch sensation. Peripheral nerves were not involved. At the time of the leucopenic episode the lesions were regressing but active.

Discussion

Rifampicin has been used widely for treatment of leprosy and tuberculosis in various dosage schedules. It is known to cause skin rashes, hepatorenal impairments, haemolytic anaemia, and 'flu' syndrome.[8–10] When rifampicin was used in combination with thiomide the incidence of hepatitis[11,12] was reported to be high. Rifampicin has been reported to have interactions[8] with many other drugs, e.g. oral contraceptives, anticoagulants and antidiabetics.

Fluoroquinolones have minimal side-effects[13,14] and they are known to cause nausea, vomiting and abdominal discomfort.[2,14,15] Cases have been reported with symptoms related to the central nervous system.[5] Ofloxacin has been widely used as a broad spectrum antibacterial agent.[16] The prescribing information indicates that leucopenia, agranulocytosis, anaemia and thrombocytopenia can occur rarely. Ofloxacin has also been reported as causing leucopenia and eosinophilia which is said to be mild and reversible.[17]

The two patients in this study developed leucopenia during the third week of therapy with a daily dose of ofloxacin and rifampicin. However this seems to be reversible as both these patients recovered completely. These patients with side-effects did not take any other drug or herbal preparations. Viral infections are known to cause leucocytopenia. However no serological test was done to rule out viral infections. Stool examination was not carried out. Serum albumin globulin reversal was observed in two out of the three patients. The significance of this is not clear. Further studies may be required.

There may be two possibilities;

a, ofloxacin might have caused bone marrow depression; and/or
b, rifampicin might have enhanced the side-effect of ofloxacin.

Drug challenge was not attempted as leucocytopenia was considered as a serious complication.

This project was a multicentre randomized double-blind controlled (field-based) clinical trial. From our centre 125 PB leprosy patients were included in the trial. Assuming that 50% of the study patients received trial regimen containing ofloxacin and rifampicin, then 3·2% of the patients who might have received this regimen had developed leucocytopenia. However it is more appropriate to compute incidence of complications among the total patients included (from all the participating centres) in this multicentre study. There has been no reports of occurrence of leucopenia after ofloxacin therapy and hence it was not possible to provide an estimate of frequency of side-effects.

Further studies are required on this aspect. However small it may be, one should carefully monitor the patients on ofloxacin therapy to identify any such complications at an early stage to avoid possible serious complications.

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