Flucloxacillin Induced Neutropenia During Treatment of Osteomyelitis

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ABSTRACT

The neutropenia was associated with a characteristic clinical sequence starting with fever, followed by generalised maculopapular rash. We report on 11 patients with Flucloxacillin induced neutropenia during treatment of acute and chronic osteomyelitis. The time of onset ranged from 10 to 14 days after beginning of treatment. The thrombo-cytopenia occurred in 8 patients.

Discontinuation of the drugs resulted in recovery from the neutropenia within 2 to 4 days. Neutropenia and concomitant symptoms should be kept in mind when treating osteomyelitis with flucloxacillin. Complete blood count and differential leukocyte count should be checked regularly during the treatment.

Flucloxacillin is penicillinase resistant, acid resistant, semisynthetic penicillin suitable for oral and parenteral use. It is active against most gram +ve cocci and because of its resistance to penicillinase, it is active against penicillinase producing staphylococci[1].

Staphylococcus aureus has been found to be the cause in about 80% of cases in most series of acute haematogenous osteomyelitis[2,3,4].

Flucloxacillin (100 to 200 mg per kilogram of body weight given daily in divided doses) by intravenous route is the drug of choice[3]. Several authors recommend the combination of cloxacillin and penicillin[2,3,5].

Neutropenia induced by B-Lactamase has been reported in about 150 patients since 1960. The neutrophil count quickly returns to normal, once treatment is stopped[6]. The basic pathogenic mechanism of this complication is not fully understood but damage seems to be limited to the more mature haemopoietic stem cells and morphologically recognisable bone marrow precursor cells, since recovery is quick on withdrawal of the drug[7].

We describe 11 patients who experienced these complications during treatment of acute or chronic osteomyelitis with Flucloxacillin.

METHODS

A study of eleven patients who developed neutropenia while they were receiving Flucloxacillin alone or combined with other antibiotics for treatment of osteomyelitis was performed. The drug was given in a therapeutic dose according to body weight and the result of culture and sensitivity (Table 1).

Seven patients were male and four were female. The age of the patients ranged from 5 years to 34 years with an average of 12 years. Six patients had acute osteomyelitis and five patients had chronic osteomyelitis.

Complete blood count (CBC), erythrocyte sedimentation rate (ESR), blood and swab culture and

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Table 1
Characteristics of patients with neutropenia induced by IV Flucloxacillin

Patient No. Age/Sex	*Treatment and Dosage (g/day)*	*Neutrophil count at admission/ at lowest 10^9/Litre*	*Platelet count at admission at lowest 10^9/Litre*	*Onset/ Duration of Neutropenia (Days)*
1. 30/M	Flucloxacillin/4 Erythromycin/2	9.6/1.2	507	14/4
2. 10/F	Flucloxacillin/2 Gentamycin/0.18	4.1/1.4	339/337	12/2
3. 28/F	Flucloxacillin/4	8.2/1.2	428/323	13/2
4. 27/M	Flucloxacillin/4	5.3/1.3	320/134	14/4
5. 6/M	Flucloxacillin/4 Kefsol/2	6/1.7	446/127	10/3
6. 24/M	Flucloxacillin/4 Gentamycin/0.24	8.8/1.25	498/142	14/4
7. 10/M	Flucloxacillin/4	7/1.85	470/126	12/2
8. 6/F	Flucloxacillin/2 Kefsol/2	8/1.25	400/120	14/4
9. 5/F	Flucloxacillin/2	8/1.2	400/135	14/4
10. 7/F	Flucloxacillin/2 Kefsol/2	6/1.3	400/146	12/3
11. 34/M	Flucloxacillin/4	8/1.9	332/127	14/4

5 patients received IV Flucloxacillin.
3 patients received IV Flucloxacillin plus IV Cephazolin (Kefsol)
2 patients received IV Flucloxacillin plus IV Gentamycin.
1 patient received IV Flucloxacillin plus oral Erythromycin

sensitivity were done on admission. CBC and ESR were repeated every fourth day. Blood culture and sensitivity were done whenever patients had a fever. Seven patients had incisional drainage and bone curettage. Four patients had no surgical treatment. One patient had sickle cell disease. All patients had normal renal and liver function tests.

RESULTS

All patients gradually developed absolute neutropenia (<2000 per cubic millilitre) after 10-14 days from the beginning of treatment (average 13 days). Eight patients developed thrombocytopenia (<200,000 per cubic millilitre) without bleeding disorder. Four patients had slight changes in platelets count. One patient had no significant change. In all patients ESR was high. Red blood cell count, haemoglobin, lymphocytes, monocytes and eosinophils were normal. Six patients grew Staphylococcus aureus from blood or wound swab. Five patients had no growth. All patients developed fever (>38°C) followed by generalised maculopapular rash one to two days prior to neutropenia. No bacterial growth was isolated from the blood. All patients responded to discontinuation of antibiotics and neutrophil counts rose to normal within two to four days.

DISCUSSION

Neutropenia is the most frequent cause of leukopenia. It is an important risk factor for infection if the counts declines below about 1,000 cells per cubic millilitre[7].

Isolated neutropenia occurring as a side effect of treatment with antibiotics of the Penicillin group have been described in about 150 patients over the past 30 years[6]. The sequence is characterised by fever followed by generalised maculopapular rash. The distribution of rash is easily confused with the rash of measles. All symptoms disappeared on withdrawal of drugs within two or four days.

Leventhal and Silken[8] reported on four patients who developed neutropenia after 20 to 30 days of drug therapy with high dose oxacillin, 200 to 400 mg/kg/day. Discontinuation of the drug resulted in resolution of the neutropenia within two or four days[8]. Brook et al, described two cases after oxacillin therapy[1]. Chu et al, presented two similar cases of neutropenia in a patient on oxacillin therapy for osteomyelitis[7]. Rouveix et al, reported 13 patients who developed neutropenia after receiving intravenous or oral B-Lactamines[6]. We think neutropenia may occur with ordinary doses of flucloxacillin.

The basic pathogenic mechanism of the complication is not fully understood, but most reports postulate either a toxic effect, dose related damage or immune mediated[9]. Thrombocytopenia may occur with treatment by B-Lactamase. Nefte reported 10 cases who developed neutropenia[10]. We think the incidence is more in our report. 8 patients developed thrombocytopenia out of 11.

The object of this paper is to remind the surgeons to consider the possibility of neutropenia if the patient develops fever, and/or generalised rash during treatment by flucloxacillin for acute or chronic osteomyelitis. The total and differential leukocyte count should regularly be checked during the flucloxacillin therapy in these patients.

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