

SEVERE LEUCOPENIA AND FEVER DUE TO BENZYL PENICILLIN — A RARE COMPLICATION OF TREATMENT WITH A COMMON ANTIBIOTIC

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SYNOPSIS

Benzylpenicillin-induced leucopenia in a patient with bacterial endocarditis is described. The leucopenia and associated fever reverted to normal once the drug was discontinued. The literature on penicillin-induced leucopenia is briefly reviewed.

INTRODUCTION

Benzylpenicillin, although one of the earliest antibiotics to be discovered, is still in common use today because of its proven efficacy and relatively low toxicity. High dose parenteral benzylpenicillin, as used for bacterial endocarditis, is rarely associated with haematological disorders. Leucopenia is an extremely unusual complication and a case is reported here.

CASE REPORT

A 32 year old Malay man was admitted for progressive heart failure, lethargy and pallor over a three month period. There was no past history of rheumatic fever or heart disease.

On examination his temperature was 37.6°C. He was pale and was in obvious heart failure. No clubbing or petechiae were noted. Clinically he had gross mitral incompetence with mild pulmonary hypertension and hepatosplenomegaly. The patient was then commenced on digoxin and frusemide with potassium supplements.

His initial investigations were: haemoglobin 10.8 gm/dl, white cell count 11,500/cmm (neutrophils 94%) and ESR 30mm/hr. Urine microscopy was normal. The ECG showed biventricular hypertrophy. There was moderate cardiomegaly on chest x-ray. An echocardiogram showed some dilatation of both right and left ventricles and there were mitral valve vegetations.

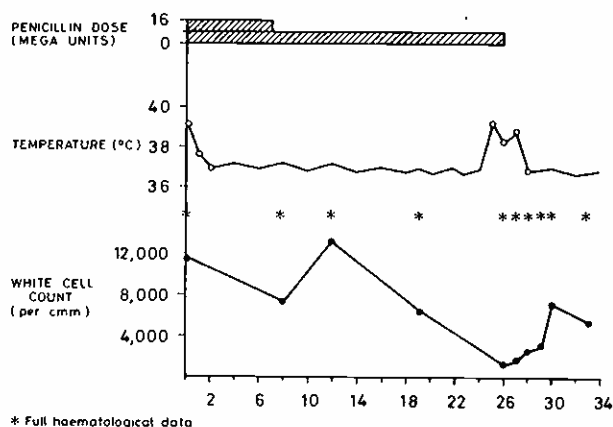
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While in the ward, his temperature ranged from 37°C to 38.4°C. On the fourth hospitalisation day, he was started on benzylpenicillin 16 mega units daily on suspicion of subacute bacterial endocarditis. This was confirmed subsequently when streptococcus viridans was cultured from his blood. His fever subsided the day after therapy began. After one week, the dose of benzylpenicillin was reduced to eight mega units daily.

On the 25th day of therapy, the patient developed a fever. There was associated anorexia, malaise and a vague generalised abdominal pain. Physical examination at this stage was essentially unchanged. No rash was noted. A blood count done the following day revealed a severe neutropenia and mild thrombocytopenia (refer to chart). His temperature ranged from 37°C to 39°C. On the 27th day of therapy the penicillin was stopped and the fever subsided the following day. Over the next two days, the white cell and platelet counts began to rise and by the third day, had reached normal limits (refer to chart).

Blood cultures repeated at this stage were negative. A coomb's test was also negative. No further antibiotic was prescribed and the patient recovered uneventfully. Besides the drugs mentioned earlier, the only other drug the patient had been on was paracetamol.



DISCUSSION

In common with the few cases reported (2, 4, 1, 3), this patient was on high dose parenteral therapy. A latent period, in this case 25 days, seemed to be essential before the development of fever and leucopenia. On stopping the antibiotic, the fever subsided promptly and his leucopenia reversed within three days. A thrombocytopenia of 76,000/cmm was also noted

*Haematological data in detail.

Days after starting penicillin	0	8	12	19	26	27	28	29	30	33
Haemoglobin (gm/dl)	10.8	11.3	10.8	12.8	11.7	12.4	12.2	13.0	12.6	12.0
White blood cells (per cmm)	11,500	7,000	13,000	6,400	1,200	1,900	2,200	2,700	6,900	5,400
Neutrophils (%)	94	64	73	60	17	8	40	—	52	56
Platelets (1000/cmm)	—	—	—	—	76	159	—	185	—	—

initially in this patient. The patient did not develop a rash although in one review (1) a maculopapular rash was noted in four out of six cases.

In the same case reports (2, 4, 1, 3), the interval between the onset of penicillin therapy and the development of leucopenia ranged from nine to eighteen days. On stopping therapy, the fever settled rapidly and the white cell counts returned to normal over two to fourteen days.

The bone marrow was not examined in this patient because of his rapid recovery after benzylpenicillin was stopped. Marrow findings in the above case reports were highly variable. They ranged from normal cellularity with decreased granulocyte precursors to maturation arrest of the granulocytes and the "post-maturation arrest" described by Joorabchi and Kohout (4) in their case which presented with a pancytopenia.

The aetiology of penicillin-induced leucopenia is debatable. Colvin et al (1) attributed it to a hypersensitivity reaction. On the other hand, Joorabchi and Kohout (4) attributed it to a "penicillin-induced blockade of the release of mature cells of all three blood elements from the marrow" thereby resulting in a pancytopenia. After their patient's blood counts had returned to normal, they were able to reproduce the pancytopenia with a single intravenous one mega unit dose of benzylpenicillin. The report of Homayouni et al (3) included cases of leucopenia due to Cephalosporin homologues and the semi-synthetic penicillins as well as benzylpenicillin. They attributed the leucopenia to a direct toxic effect of the high dose antibiotic. After their patients' white cell counts had returned to normal, they were able to restart the same antibiotic at a lower dosage with no further ill effects. Different mechanisms therefore, seem to be responsible for penicillin-induced leucopenia.

CONCLUSION

A case of benzylpenicillin induced leucopenia is reported here. This rare complication is related to the use of the antibiotic in high parenteral dosages. Since these antibiotic regimes are used to treat serious, life-threatening infections, the recurrence of fever with leucopenia during a course of treatment will always be a cause of alarm. If benzylpenicillin induced leucopenia is borne in mind, unnecessary investigations may be avoided. Perhaps twice weekly blood counts whenever high dose parenteral antibiotics are used will alert the physician to the imminence of antibiotic-induced leucopenia.

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