Myelotoxicity of D-penicillamine

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SUMMARY Information has been collected on 10 patients, 9 with marrow depression and 1 in whom the diagnosis was presumed. Six of the 10 patients died. The sequentially recorded blood counts on at least 5 of the patients showed a downward trend of the white cell and platelet counts while D-penicillamine was still being administered. One patient suddenly developed leucopenia and thrombocytopenia with a streptococcal septicaemia.

Blood dyscrasias are among the more serious adverse effects associated with the administration of D-penicillamine (Bird, 1974; Barnett and White-side, 1976). Agranulocytosis (Corcos *et al.*, 1964; Nahir and Scharff, personal communication) and thrombocytopenia (Multicentre Trial Group, 1973; Harrison and Hickman, 1976) have also been reported but will not be discussed further in this communication. Fourteen out of 18 deaths ascribed to D-penicillamine reported to the Committee on Safety of Medicines (CSM) between January 1964 and December 1977 were apparently due to blood dyscrasias, at least seven of them marrow aplasias (Committee on Safety of Medicines, personal communication).

Patients and methods

We have collected information on 10 patients (Table 1), 9 with marrow depression and 1 whom the diagnosis was presumed (case 10) but who died before the marrow had been examined. There were

5 men and 5 women, with a mean age of 59 years (range 35-68). The duration of rheumatoid disease ranged from 2 to 35 years, and at least 6 of the patients were seropositive for rheumatoid factor. All the patients had been treated with D-penicillamine, 9 for rheumatoid arthritis and 1 for scleroderma, for a mean period of 16 months (range 3-60). The mean dose of D-penicillamine at the time of marrow depression was 615 mg per day (range 250-1000). Reports on 3 of the patients have already been published (Richards *et al.*, 1976; McAllister and Vale, 1976; Bourke *et al.*, 1976), and 3 of the cases had been reported to the CSM.

Results

Six of the 10 patients died. Those who survived were given supportive treatment, and the marrow gradually recovered over a period of up to 1 year. In most of these cases the interval between blood counts before the recognition of marrow depression was a month or less (Figs. 1-8). Two of the patients, whose charts are not shown, had their blood monitored less frequently, but in each case the last recorded blood count before the recognition of marrow

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Table 1 Basic data on 10 patients developing marrow depression associated with the administration of D-penicillamine.

Case no.	Sex	Age/yr	Diagnosis	DAT	Duration/yr	Dose/mg	Treatment/ months	Outcome
1	M	68	RA	NS	NS	1000	18	A
2	M	68	RA	+ve	2 yr	450	17	D
3	F	66	RA	+ve	18 yr	600	2-3	D
4	F	54	RA	+ve	15 yr	250	17	D
5	F	52	Scleroderma	—	23 yr	500	6	D
6	M	63	RA	+ve	2 yr	750	4	A
7	M	54	RA	+ve	30 yr	500	12	A
8	F	35	RA	NS	35 yr	900	60	D
9	F	68	RA	NS	NS	450	9	A
10	M	62	RA	+ve	2 yr	750	12	D

Fig. 1 Case 1. Gradual onset of marrow depression more than 1 year after start of treatment with D-penicillamine.

Fig. 2 Case 2. Gradual onset of marrow depression more than 1 year after start of treatment with D-penicillamine.

depression was well within the normal range. The sequentially recorded blood counts of 5 of the patients showed a downward trend of the white cell and platelet counts while D-penicillamine was still being administered (Figs. 1, 4, 5, 6) and a similar but less striking trend was apparent in the counts of 2 other patients (Figs. 2 and 3). A fall in the polymorph-neutrophil count in 2 of the patients (Figs. 5 and 6) preceded the reduction in the total white cell count; in both these patients relative granulocytopenia developed during the first 6 months of treatment. One patient (Fig. 7) who had been on D-penicillamine 450 mg per day for approximately 9 months developed marrow depression after a small increase in dosage. Case 10 (Fig. 8) differed from the others in showing no premonitory fall in the blood count, which was normal within a fortnight of his death from streptococcal septicaemia following cellulitis; a mild eosinophilia had been apparent on several occasions during the last 3 months of treatment.

All of the patients had received a number of drugs

Fig. 3 Case 3. Marrow depression developing during the first 4 months of treatment with D-penicillamine in a patient with a previous history of thrombocytopenia associated with chrysotherapy.

Fig. 4 Case 4. Marrow depression 18 months after starting treatment with D-penicillamine. The patient had previously had both gold and D-penicillamine treatment stopped because of skin rashes.

Fig. 5 Case 5. Marrow depression presenting with polymorph neutropenia during the first 6 months of D-penicillamine treatment.

over the years preceding treatment with D-penicillamine. Four patients had received chrysotherapy, and in 3 of them the drug had been withdrawn because of an adverse effect; 2 had developed a rash and 1 thrombocytopenia. Another of the patients had phenylbutazone added to her treatment 2 months before developing marrow hypoplasia. Concurrent therapy with other antirheumatic/anti-inflammatory drugs was a feature in the majority of the patients, but full drug histories were not always available.

Discussion

The mechanism of marrow hypoplasia developing in patients on D-penicillamine is not fully understood, but interference by the drug with the synthesis of DNA has been suggested (Chandra and Koch, 1975). The findings in 7 of the patients in this series suggest that the onset of marrow depression associated with the administration of D-penicillamine

is usually gradual, which is consistent with a direct toxic effect on the marrow. A fall in the platelet count within the normal range has been observed in patients treated with D-penicillamine (Weiss *et al.*, 1978). Leucocytosis and thrombocytosis (Selroos, 1972; Hutchinson *et al.*, 1976), often observed in active rheumatoid disease, usually settles with the onset of spontaneous or induced remission. In D-penicillamine treated patients this may therefore be due to either a direct or an indirect effect on haemopoiesis. The exact level at which a blood count becomes abnormally low cannot be stated; the persistence, rate, and degree of fall must all be taken into consideration. Plotting the results of blood counts on a semi-logarithmic scale helps to reveal a downward trend (Golton, 1960) and is a routine procedure in oncological practice.

Sudden onset of marrow aplasia associated with D-penicillamine therapy has also been reported (Barnett and Whiteside, 1976; Jaffe, 1977-8; Weiss *et al.*, 1978). In case 10 the onset of presumed marrow hypoplasia was sudden and associated with an

Fig. 6 Case 6. Marrow depression presenting with polymorph neutropenia during the first 6 months of D-penicillamine treatment.

overwhelming streptococcal infection. It is possible that haemopoiesis may have already been impaired but that the onset of marrow failure became apparent only with increased consumption of leucocytes and platelets associated with the acute infection.

It has been suggested that marrow depression may be more common in patients who have previously been treated with gold (Webley and Coomes, 1978), as had at least 4 of the patients in our series, 1 of the patients had developed thrombocytopenia and 2 of them rashes during chrysotherapy. There is of course a high probability that any patient with long standing rheumatoid disease will have at sometime been exposed to gold treatment.

Fig. 7 Case 7. Marrow depression developing after a small increase in D-penicillamine dosage with rapid recovery after withdrawal of the drug.

Fig. 8 Case 10. Sudden onset of presumed marrow failure associated with a streptococcal septicaemia in a patient on treatment with D-penicillamine.

The practice of giving lower doses of D-penicillamine and allowing longer intervals between dose increases is now recommended. Jaffe (1977-8) observes that the rate of dose increment appears to be more important than the absolute dose in determining the development of certain side effects. Hill (1977) has also suggested that adverse effects are dose related.

It is concluded that marrow depression developing in patients on D-penicillamine, although it can develop suddenly, is more usually of gradual onset. Trends in the white cell and platelet count moving through the normal to the low normal range should be recognised as important signs of impending marrow failure. It is also suggested that haemopoiesis may be impaired in patients on D-penicillamine in the presence of a normal blood count, so that the marrow is unable to respond to a sudden demand for increased output. Careful monitoring of blood counts combined with the use of the lowest effective dose of D-penicillamine should do much to reduce the frequency of drug induced aplasia.

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