DAPSONE-INDUCED HAEMOLYSIS

BY

C. D. R. PENGELLY, M.D., M.R.C.P., M.R.C.P.Ed.

Consultant Physician, North and Mid-Cheshire Hospital Group; Honorary Research Worker in Haematology, Manchester Royal Infirmary

Dapsone, a sulphone, is effective in the treatment of leprosy and of dermatitis herpetiformis. Its toxic effects include haemolytic anaemia. Goodman and Gilman (1955b) state that haemolytic anaemia occurs to a varying degree in practically every patient taking sulphone drugs, whereas Martindale (1958) says that haemolytic anaemia due to dapsone is rare. The two statements would be compatible if Goodman and Gilman had said "haemolysis" instead of "haemolytic anaemia," for a considerable degree of haemolysis has to occur to cause actual anaemia, provided that the bone-marrow function is not impaired (Crosby and Dameshek, 1955). Frank anaemia must be rare in dapsone-treated patients, for it is not even mentioned in a report about 10,000 lepers receiving the drug (Garrett and Corcos, 1952), though anaemia of unspecified type has been recognized (Allday and Barnes, 1951; Lowe and Davey, 1951; Dharmendra and Chatterji, 1953; Gilbert, 1953; Kruizinga and Hamminga, 1953; Alexander, 1955; Morgan *et al.*, 1955; Garrett, 1956) and sometimes evidence of haemolysis (Lowe, 1950; Ramanujam and Smith, 1951; Smith and Alexander, 1959; Arnold, 1962). Smith and Alexander (1959) noted Heinz bodies in the red cells of four patients taking 100 to 200 mg. of dapsone daily.

This paper reports the cases of four patients taking dapsone for dermatitis herpetiformis and of one normal subject to whom dapsone was given as an experiment. None had significant anaemia but all showed reduced red-cell life-spans.

Methods

Red-cell survival was estimated with ^{51}Cr , using the method of Mollison and Veall (1955), applied as described by Pengelly and Wilkinson (1962). The red-cell volume was repeated at the end of the survival test only once (the first time in Case 1), at which time it was being estimated routinely with ^{32}P . There was an insignificant change (less than 5%). There was no reason to believe that any significant change in red-cell volume had occurred during any of the other survival tests.

Blood was exposed to $\text{Na}_2^{51}\text{CrO}_4$ solution in acid-citrate-dextrose for 40 minutes, about 60 microcuries being injected after washing the red cells three times with 3% plasma saline. Venous blood samples were taken from the opposite arm at 20- and 30-minute intervals, packed cell volumes were estimated and corrected for trapped plasma by the method of Chaplin and Mollison (1952), and the blood was then haemolysed with saponin. Radioactive counting was done with a scintillation counter type N.550 and scaler type N.529 (Ekco Electronics Ltd.) with a voltage of 1,250 and discriminator bias of 20. A minimum of 10,000 counts was taken from each blood sample. The counts of the blood specimens were expressed in terms of 100% red cells and the average was taken as the 100% radio-chromium (^{51}Cr) level. Thereafter blood samples were taken twice weekly, and after allowance for radioactive decay the counts were expressed as a percentage of the initial ^{51}Cr level. Samples were taken at least until the "half chromium time" was reached. If the curve of ^{51}Cr loss from the red cells fell below the normal range (Pengelly and Wilkinson, 1962) then the curve was corrected for ^{51}Cr elution by method A (Mollison, 1956), which assumes the

normal red-cell life-span to be 110 days, and the results were plotted on arithmetical graph paper. Mean red-cell life-span was estimated by extrapolating the line so obtained to cut the baseline. Occult blood tests on the stools were done by the modified Gregerson method of Needham and Simpson (1952).

Patients Investigated and Results

Case 1

Male typographer aged 39 (in 1957). Gastrectomy for duodenal ulcer 1942; dermatitis herpetiformis since 1953, controlled with dapsone 150 mg. daily. Referred to Dr. William Brockbank at Manchester Royal Infirmary in December, 1957, with anaemia and mild recurrent jaundice. Investigations: Hb 60% (100% = 14.6 g./100 ml.); M.C.H.C. 26%; serum iron 20 $\mu\text{g.}/100\text{ ml.}$; serum bilirubin 1.6 mg./100 ml.; no evidence of significant gastro-intestinal blood loss. Oral iron therapy raised the haemoglobin to 90%, but the recurrent jaundice continued and he was admitted to hospital in October, 1958.

Examination showed slight jaundice, spleen tip just palpable; otherwise nothing significant. Two occult blood tests on the stools, both negative; Hb 80%; serum bilirubin 4.8 mg./100 ml.; thymol turbidity, zinc turbidity, alkaline phosphatase, and plasma proteins normal; reticulocytes 5%; faecal urobilinogen 225 mg./100 g.; urinary urobilinogen not increased; saline fragility of red cells normal; sternal-marrow smear showed increased erythropoietic activity; Heinz bodies seen occasionally in red cells; direct Coombs test negative; no methaemoglobin demonstrated in blood; glucose-6-phosphate dehydrogenase activity and glutathione stability of red cells normal. Approximate red-cell life-span (^{51}Cr) was 29 days. An attempt to change the dapsone therapy to sulphamethoxypyridazine was unsuccessful, and he was discharged without any change in his treatment. Since then he has had several episodes of mild right subcostal pain, but two cholecystograms have been normal.

In 1962, on hearing that Case 2 had successfully been taken off dapsone he made another attempt to replace it with sulphamethoxypyridazine and managed to reduce the dapsone to 100 mg. daily while also taking 1 g. of sulphamethoxypyridazine daily. A repeat red-cell survival test gave an approximate red-cell life-span of 32 days.

Case 2

Retired engineer aged 74. Referred to my out-patient clinic at Altrincham General Hospital in May, 1961, with low back pain for which no cause could be found and which vanished without treatment. Dermatitis herpetiformis for four years controlled with dapsone 100 mg. daily. Previous history of cardiac infarction. Examination showed marked arteriosclerosis; otherwise negative. No splenic enlargement. Three tests for occult blood in the stools were negative; Hb 81%; colour index 1; saline fragility of red cells normal; blood film showed an occasional spherocyte and polychromatic red cell; serum bilirubin, thymol turbidity, zinc turbidity, alkaline phosphatase, and plasma proteins normal; reticulocytes 6%; direct Coombs test negative; sternal-marrow smear showed increased erythropoietic activity; no Heinz bodies and no methaemoglobin demonstrated in blood; glucose-6-phosphate dehydrogenase activity and glutathione stability of red cells normal. Approximate red-cell life-span (^{51}Cr) was 35 days. Subsequently sulphamethoxypyridazine 0.5 g. twice daily was given instead of dapsone, and a repeat red-cell survival curve (three months later) fell within the normal range (Pengelly and Wilkinson, 1962). The patient was admitted as an emergency case to Altrincham General Hospital on April 7, 1962, with

a right hemiplegia, and died five days later. Necropsy showed a recent cardiac infarct with mural thrombosis and cerebral embolism. There was no abnormality of the liver, spleen, or bone-marrow.

Case 3

Female student aged 24. Dermatitis herpetiformis for four years, controlled by dapsone 300 to 400 mg. a week. Investigated by me by courtesy of Dr. G. K. Hargreaves, consultant dermatologist. Examination showed no splenic enlargement. Three tests for occult blood in stools—one weakly positive, two negative; Hb 85%; C.I. 1; blood film normal; reticulocytes 2%; serum bilirubin, thymol turbidity, zinc turbidity, alkaline phosphatase, and plasma proteins normal; direct Coombs test negative; no Heinz bodies and no methaemoglobin demonstrated in blood; glucose-6-phosphate dehydrogenase activity and glutathione stability of red cells normal. Approximate red-cell life-span (^{51}Cr) was 46 days. An attempt to change the dapsone to sulphamethoxy-pyridazine was not successful.

Case 4

Housewife aged 28. Dermatitis herpetiformis for 14 years controlled with dapsone 50 mg. daily. Investigated by me by courtesy of Dr. G. K. Hargreaves. Examination showed no splenic enlargement. Two stool tests for occult blood were negative; Hb 75%; C.I. 0.9; blood film showed slight hypochromia; reticulocytes 3%; direct Coombs test negative; serum bilirubin, thymol turbidity, zinc turbidity, alkaline phosphatase, and plasma proteins normal; no Heinz bodies and no methaemoglobin demonstrated in blood; glucose-6-phosphate dehydrogenase activity and glutathione stability of red cells normal. Approximate red-cell life-span (^{51}Cr) was 48 days. An attempt to change the dapsone to sulphamethoxy-pyridazine was not successful.

Case 5

Normal healthy Indian man aged 31. Red cells were labelled with ^{51}Cr on May 14, 1962, and ^{51}Cr loss was followed by blood samples taken every two to three days for ten days. Dapsone was then given daily for 19 days (total dose 2,050 mg.). The curve remained normal for 22 days, then fell below the normal range (see Chart). A summary of the results is shown in the Table.

Case 5 (normal healthy subject). Effect of dapsone on red-cell survival. The stippled area represents the normal range of ^{51}Cr loss from the red cells (Pengelly and Wilkinson, 1962).

Case No.	Dapsone Dosage (mg./day)	Haemoglobin (%) (100% = 14.6 g./100 ml.)	Mean Red-cell Life-span (Days)
1	{ 150 100	80 80	29 32
2	{ 100 Nil	80 84	35 Normal*
3	57†	85	46
4	50	75	48
5	100‡	95	Reduced§

* See paragraph on methods. † Average dose 400 mg./week. ‡ Total dose 2,050 mg. in 19 days. § See Chart.

Discussion

Four patients having dapsone therapy for dermatitis herpetiformis have been investigated for haemolysis with ^{51}Cr and all were found to have a reduced red-cell life-span. Although there was reason to believe that haemolysis might be found in Cases 1 and 2 because of the jaundice in the first and the blood-film appearances in the second, this was not so in Cases 3 and 4, in which the only evidence of haemolysis was the reduced red-cell life-span. It seemed probable, therefore, that Goodman and Gilman (1955) were correct in suggesting that practically every patient taking sulphone drugs has haemolysis. Dapsone was then shown to cause a shortened red-cell life-span in a healthy subject (Case 5).

The mechanism of this haemolysis is not clear, though the evidence from Case 5 is that the dapsone has an effect on the mature red cells. The shape of the survival curves was of no help in deciding whether destruction was due to a premature ageing process or to random destruction, as the points gave as good a straight line on a semilogarithmic plot as on an arithmetical one, but this was previously found when destruction was apparently due to antibody (Pengelly and Wilkinson, 1962). Desforges *et al.* (1959), however, using radioactive iron, demonstrated a reduction of the life-span of all red cells of a single age-group to about 50 days in one patient taking sulphoxone, which is converted into dapsone in the body (Goodman and Gilman, 1955a).

There was no abnormality in glucose-6-phosphate dehydrogenase activity or of glutathione stability of the four patients' red cells. There was a suggestion from the results that a quantitative relationship may exist between the dose of dapsone and the degree of shortening of the red-cell life-span.

Summary

Four patients taking different doses of dapsone for dermatitis herpetiformis were tested for erythrocyte survival with ^{51}Cr . All showed a diminished red-cell survival. In only two was there any previous suggestion of a haemolytic state and in both the haemoglobin level was about 80%. Glucose-6-phosphate dehydrogenase activity and glutathione stability of the red cells were normal in all the patients.

Proof that dapsone causes haemolysis of mature red cells in a healthy subject was obtained by following the survival of his ^{51}Cr -labelled red cells without dapsone administration for 10 days and then giving him the drug.

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DESENSITIZATION FOR DAPSONE DERMATITIS

BY

S. G. BROWNE, M.D., F.R.C.P., F.R.C.S., D.T.M.

Leprosy Service Research Unit, Uzuakoli, Eastern Nigeria

Sensitivity to dapsone occurring in a definite though inconstant proportion of leprosy patients is a well-recognized disadvantage of sulphone therapy. The unidentified allergen may be a modified sulphone molecule or a breakdown product formed in the liver. Some aspects of this sensitivity and of successful attempts at desensitization may be of interest to other workers besides leprologists.

Presenting Features

The commonest presenting features of sensitivity to dapsone are seen in the skin. Their gravity ranges from a relatively banal type of fixed eruption characterized by a few hypermelanotic macules (Browne, 1959) to a widespread bullous eruption proceeding to ulceration. On the other hand, a generalized sensitization of the skin may occur, with a diffuse papular irritating eruption—the “fifth-week dapsone dermatitis” of the early days of (high-dosage) sulphone therapy—which may be succeeded by a fatal exfoliative dermatitis (Allday and Barnes, 1951; Garrett, 1951; Barnes and Barnes, 1951) or by a widespread post-inflammatory hypermelanosis. If the superficial strata of the epidermis are sensitized, then cleavage may show itself clinically by toxic epidermal necrolysis (Browne and Ridge, 1961).

In addition to these cutaneous manifestations there may be systemic symptoms of serious import, such as persistent pyrexia (“drug fever”), severe generalized malaise, albuminuria, toxic hepatitis, lymphadenopathy (rarely proceeding to suppurative adenitis), leucopenia, severe and progressive anaemia, and acute psychosis. Any sign of sensitivity, cutaneous or systemic, may recur on subsequent ingestion of dapsone even in very low doses (of the order of 0.01 g. or less), or of a drug acting parallergetically. Such subsequent episodes may be more serious than the original reaction, and are sometimes fatal.

While sulphone dermatitis is probably of less frequent occurrence now than formerly, yet it still accounts in the aggregate for a considerable toll of suffering, and necessitates the interruption—or even the definitive suppression—of anti-leprosy treatment. The condition may arise within a few minutes of the ingestion of the first standard dose of 0.1 g. of dapsone. In patients who have had no access to clandestine supplies of the drug, the possibility of sensitization from a previous dose can be excluded, though parallergetic sensitization with a sulphonamide cannot always

be ruled out. More often, however, it appears after a few weeks of therapy on standard regimens of gradually increasing doses—that is, 0.1 g. twice weekly for three to four weeks, rising to 0.2 g. and then to 0.3 g. for similar periods, before attaining a maximum of 0.4 g. twice weekly for a patient weighing over 140 lb. (63.5 kg.).

Parallergetic dermatitis may occur in which a closely related compound—for example, diamino-diphenyl sulphoxide (Browne and Davey, 1961) or a sulphonamide—is implicated; more rarely, a chemically unrelated compound used in leprosy treatment—for example, thiambutosine or ditophal—or even a barbiturate or an antihistaminic, may provoke an immediate recurrence of generalized dermatitis in a patient primarily sensitized by dapsone.

When sensitivity to dapsone takes the form of the classical “fixed eruption,” with one or more hypermelanotic macules of skin and, rarely, of mucosae (labial, nasal, buccal, urethral, conjunctival), continued medication may not always result in exacerbation of the individual lesions, and anti-leprosy treatment may be continued without danger or inconvenience. In such cases there may be a “hardening” or a reduction in sensitivity similar to that reported by Hellier (1958) in sensitization by contact, and capable of mechanical or immunological explanation, possibly with a psychological component.

Recourse may sometimes be had successfully to a second-line drug, such as thiambutosine (a diphenylthiourea) or thiacetazone (a thiosemicarbazone), to which the patient may prove to be non-sensitive.

The Literature

Opinion regarding desensitization in patients sensitive to sulphonamides is divided. Tate and Klorfajn (1944a, 1944b) reported some successful attempts, but were unable then to assert that their results were permanent or that the procedure used could be generally adopted. In the same year Park (1944a, 1944b) also reported successful desensitization of two patients, in one of whom, however, partial sensitivity returned. In the experience of some subsequent workers such methods of slow desensitization for sulphonamide sensitivity may be successful, but others agree with the conclusion expressed by Goodman and Gilman (1955) that “effective desensitization procedures are unknown.” Attempts to achieve desensitization may