

Permanent retinal damage following massive dapsone overdose

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SUMMARY A massive dose of 7.5 g of 4,4'-diamino, diphenyl sulphone (dapsone) taken as a suicide attempt in a patient on long-term therapy for tuberculoid leprosy resulted in permanent bilateral retinal necrosis, a previously unreported side effect of this drug. The patient developed a severe haemolytic anaemia, methaemoglobinaemia, and acute renal failure requiring peritoneal dialysis. It is proposed that the retinal damage was due to a combination of severe hypoxaemia and the physical effects of red cell fragmentation producing vascular occlusion in the macular and perimacular region, with consequent ischaemic necrosis.

4,4'-Diamino, diphenyl sulphone (4,4' DDS) has been used in the treatment of leprosy since 1941. Reported side effects are predominantly haematological, and include methaemoglobinaemia, agranulocytosis, and haemolytic anaemia.¹⁻⁵ However, overdoses of dapsone have rarely been described.⁶⁻⁸ The present case report describes a massive overdose of 4,4' DDS taken as a suicide attempt. Side effects included previously unreported permanent macular damage.

Case report

A 31-year-old Burmese man was admitted to Royal Perth Hospital in October 1978 having ingested a total of 7.5 g of 4,4' DDS in a suicide attempt. The drug was commenced in 1975 for tuberculoid leprosy, histologically confirmed on skin biopsy, and the patient had been maintained on 50 mg daily before admission. Physical examination on admission revealed an ill-looking man with obvious bluish-grey cyanosis of the tongue, lips, and extremities. The pulse was 108/min and the blood pressure 130/85 mmHg. The remainder of the general examination, including ophthalmoscopy, revealed no abnormality. Blood obtained at venesection was a dark chocolate brown colour and on analysis yielded a total haemoglobin content of 145 g/l and a methaemoglobin of 46 g/l. The blood urea was 7.1 mmol/l (normal 3-8) and the creatinine 111 μ mol/l (normal 50-120). The urine was a deep wine red colour,

and free haemoglobin was present, with no red cells seen on microscopical analysis.

Four days after admission to hospital the haemoglobin level had fallen precipitously to 78 g/l and the white blood cell count had risen to $38.5 \times 10^9/l$. A peripheral blood film was consistent with a severe haemolytic process, showing crenated, distorted, and fragmented cells, polychromasia, Howell-Jolly bodies, and grossly dysplastic erythroblasts. A coagulation profile was normal. Although initial screening tests for the presence of glucose-6-phosphate dehydrogenase deficiency were negative, subsequent follow-up studies disclosed the milder form (type A) of the condition.

The subsequent clinical course of the patient was one of massive intravascular haemolysis, requiring transfusion with 6 units of packed red blood cells, and severe methaemoglobinaemia (Fig. 1), which was treated with methylene blue and ascorbic acid intravenously. Acute renal failure supervened eventually, requiring peritoneal dialysis (Fig. 2). The patient remained critically ill for over a week and required vigorous supportive therapy. Two weeks after admission he complained of blurred vision. Visual acuity was 6/36 in each eye with no significant refractive error. The ocular abnormalities were confined to the posterior pole of the retina of each eye, and consisted of a bilateral yellow-white appearance of the retina in the macular and paramacular region, with several minute intraretinal haemorrhages in the adjacent normal retina. There was no macular oedema or serous retinal detachment. Fluorescein angiography showed nonperfusion in the region of the yellow-white retina, with

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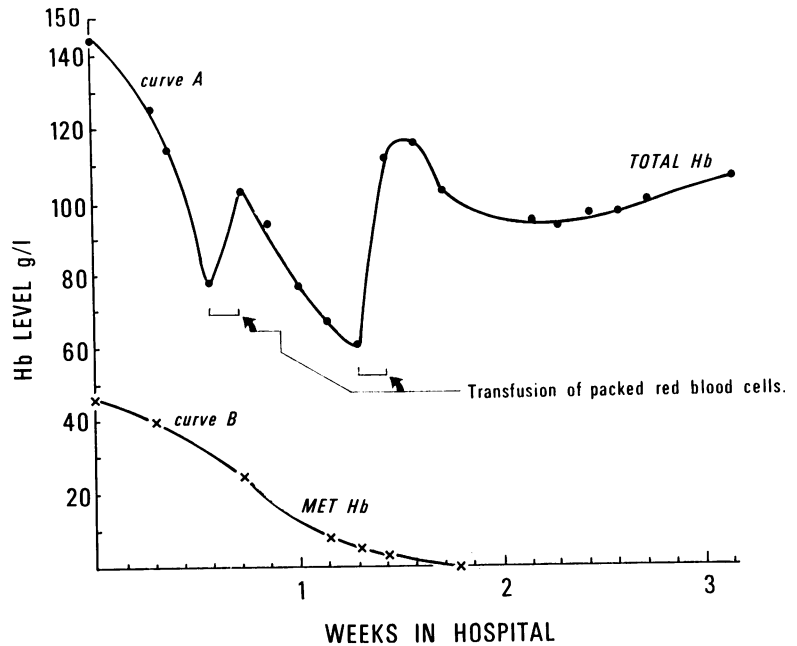


Fig. 1 Changes in the total haemoglobin level (curve A) and methaemoglobin level (curve B) during hospital admission.

abrupt termination of the venules and arterioles surrounding the site (Fig. 3). Normal perfusion was present in the retinal periphery, which was also ophthalmoscopically normal.

It was thought that the ophthalmoscopic appearance of the macula and the fluorescein angiogram

changes indicated that necrosis of the macular region had taken place. The patient was started on systemic prednisolone therapy, 75 mg per day for 1 week, and then on a reducing dosage for 1 month. During the course of the next 3 weeks the yellow-white appearance of the macula faded and was

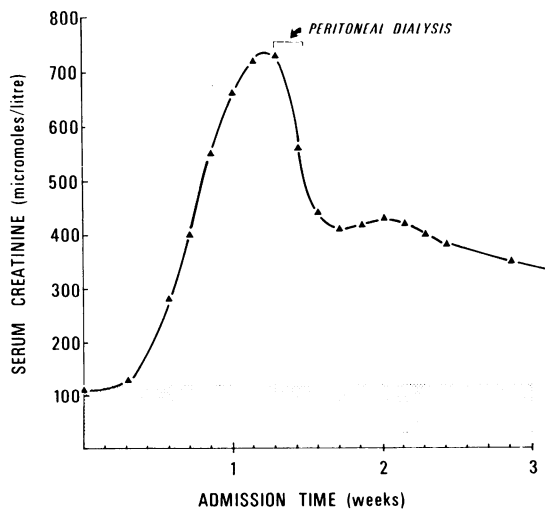


Fig. 2 Changes in serum creatinine level during hospital admission. Arrowed bracket indicates peritoneal dialysis. Shaded area represents the normal range of serum creatinine.

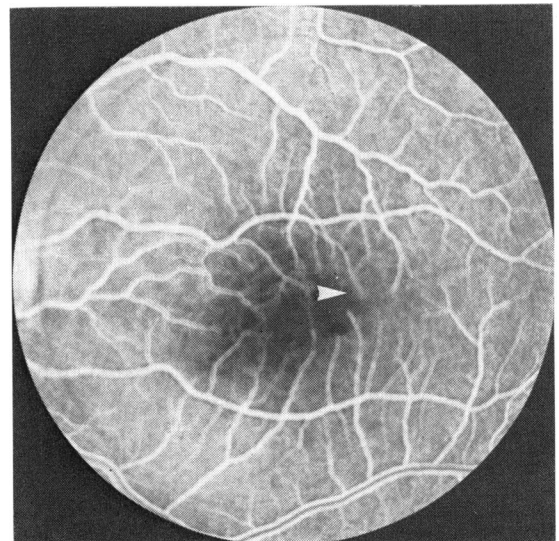


Fig. 3 Fluorescein angiogram of left eye 2 weeks after the acute episode showing capillary closure in the paramacular region with abrupt termination of the arterioles and venules (arrowed).

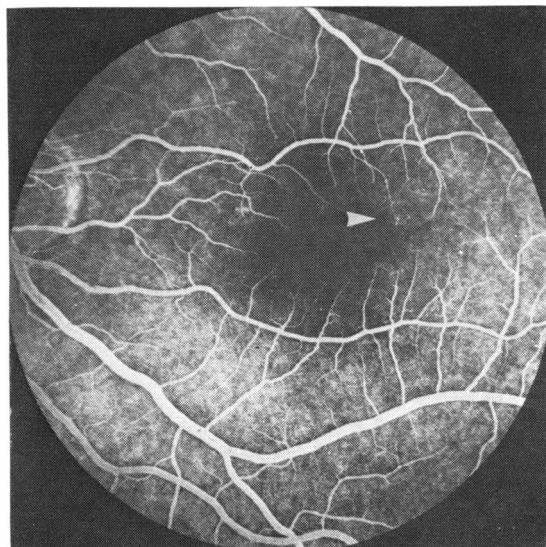


Fig. 4 Fluorescein angiogram of left eye 7 months after the acute episode. Revascularisation of the paramacular region has occurred, with the development of an abnormal looped vessel on the edge of the previously avascular zone (arrowed).

replaced by the more normal orange colouration. The normal macular light reflex and luteal pigment did not reappear, and there was a minimal pigmentary change in the retinal pigment epithelium. Three weeks after the blurred vision had been noted the visual acuity had improved to 6/18 in each eye, and no further improvement has occurred. Fluorescein angiography 7 months after the event showed revascularisation of the macula and the perimacular region. In the left eye, on the edge of what was the avascular zone, an abnormal looped blood vessel had appeared (Fig. 4).

Discussion

The absence of retinal damage in other cases of dapsone poisoning⁶⁻⁸ and the restriction of the retinal necrosis to the macular region in this patient, makes a direct toxic effect of the dapsone unlikely. It is more probable that the macular damage was ischaemic in origin from a combination of acute severe peripheral hypoxaemia and the physical effects of red cell fragmentation, consequent upon the haemolytic process, interfering with the macular blood supply.

The haematological side effects of dapsone include methaemoglobinaemia, agranulocytosis, and haemolytic anaemia,¹⁻⁵ which is usually mild but may be more severe in the presence of glucose-6-phosphate dehydrogenase deficiency.³ Haemolysis

is probably due to intracellular oxidant activity of the drug.⁴ Probably in this patient the equivalent of the total red cell circulating mass was haemolysed, and the rate of haemolysis appeared unaffected by transfusion (Fig. 1). It can be inferred that almost all the red cells were damaged and therefore potentially defective in terms of oxygen carrying capacity. In addition, on admission to hospital a methaemoglobin level of 46 g/l, representing some 40% of the total haemoglobin, was present (curve B, Fig. 1), which would have had the effect of even further lowering the potential blood oxygen-carrying capacity. Thus it seems likely that profound tissue hypoxia was present in this patient, probably when he was admitted to hospital. We believe that this profound hypoxia was a major aetiological factor in the macular changes observed.

The physical effects of red cell fragmentation causing macular vascular occlusion may also have been a significant factor. The macula nonperfusion seen on the fluorescein angiogram is similar to the macular vascular changes reported in sickle cell disease.⁹⁻¹² This effect has been attributed to a sludging effect of the sickled red cells,¹³⁻¹⁷ and the macular capillaries may be especially susceptible owing to their small calibre and considerable length.¹⁸ Fragmented red cells are regularly seen in patients on dapsone, particularly at dosage levels of 100 mg and above,¹⁹ but the cause is unclear; it does not appear to be related to microangiopathy or mechanical trauma. Although central vision can be preserved in the presence of macular capillary closure,^{10 11 20 21} the red cell fragmentation consequent upon the massive haemolysis combined with the severe hypoxaemia may have been sufficient to produce macular changes. The abnormal looped vessel on the edge of the previously avascular area (Fig. 4) is of interest. It probably represents abnormal blood vessel regeneration and is similar to some of the perimacular vascular changes seen in sickle cell disease.¹¹

If a massive overdose of dapsone with intravascular haemolysis and a sickle cell crisis are comparable events, it is possible that dapsone at normal dosage levels may produce foveal capillary changes similar to the usually asymptomatic foveal vascular disruption seen in 29% of patients with sickle cell disease.¹¹ We conclude that all patients experiencing blurred vision while on dapsone therapy should therefore be subjected to careful assessment of their macular function, including fluorescein angiography. Our experience would also suggest that physicians would be wise to screen patients for the presence of glucose-6-phosphate dehydrogenase deficiency before embarking upon therapy with dapsone.

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