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, methaemoglobinemia, 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 methaemoglobinemia, agranulocytosis, and haemolytic anaemia. However, overdoses of dapsone have rarely been described. 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 µmol/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 38·5×10⁹/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 methaemoglobinemia (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 para-macular 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...
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

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

**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).
replaced by the more normal orange colouration. The normal macular light reflex and luteal pigment did not reappear, and there was a minimal pigmen-
tary 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 poisoning and the restriction of the retinal
damage 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
methaemoglobinemia, agranulocytosis, and hae-
molytic anaemia, which is usually mild but may be
more severe in the presence of glucose-6-
phosphate dehydrogenase deficiency. Haemolysis
is probably due to intracellular oxidant activity of
the drug. 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. This effect has been attributed to a
sludging effect of the sickled red cells, and the
macular capillaries may be especially susceptible
owing to their small calibre and considerable
length. Fragmented red cells are regularly seen in
patients on dapsone, particularly at dosage levels of
100 mg and above, 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, 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 abnor-
mal blood vessel regeneration and is similar to some
of the perimacular vascular changes seen in sickle
cell disease.

If a massive overdose of dapsone with intra-
vascular 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. 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 angeo-
graphy. 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.
References

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