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DEATHS IN PATIENTS RECEIVING ORAL IRON CHELATOR L1

Agarwal *et al* (1992) reported four deaths in Indian thalassaemics while on the oral iron chelator L1 or shortly after discontinuing it. While their conclusion was that none of the deaths was related to L1 in any way, despite our evidence to the contrary in one of them (Mehta *et al*. 1991), new evidence (Berdoukas *et al*, 1993) would appear to suggest otherwise.

Preclinical animal studies have shown thymic and other organ atrophy in rats at doses of 100 mg/kg or more (Berdoukas *et al*, 1993). One of the patients from the group of Agarwal *et al* (1992), who died of overwhelming varicella infection in Philadelphia, was found to have thymic atrophy (Berdoukas *et al*, 1993). It is quite likely that the fatal varicella infection was the result of L1-induced atrophy of lymphatic organs and immunosuppression.

Another splenectomized patient who had not been vaccinated against pneumococcus and who was not on penicillin prophylaxis died of pyogenic meningitis. The third patient, who was vaccinated against pneumococcus prior to splenectomy and was on penicillin prophylaxis, died of an acute gastrointestinal infection with possible encephalitis within 24 h of presentation. The causative organism in either case, if identified, was not mentioned. Even if the organism was pneumococcus, it is possible that L1-induced immunosuppression (and resultant hypogammaglobulinaemia) could have increased the patients' susceptibility to the infections.

The death of the fourth patient was attributed to cardiac failure, arrhythmia, urinary sepsis, and septicaemia by Agarwal *et al* (1992). As physicians who looked after the patient during his terminal illness, we have reported our strong belief that the patient died of consequences of L1-induced systemic lupus erythematosus (Mehta *et al*, 1991). There was no documented cardiac arrhythmia, and the symptoms of the urinary tract infection had improved on therapy prior to death. The blood pressure of 170/120 recorded 10 min prior to death is incompatible with septic shock. Berdoukas (1991) initially felt that the death may have been due to the cardiac effects of the high-dose methylprednisolone that the patient was receiving, but has now hypothesized (Berdoukas *et al*, 1993) that cardiac dysfunction may have been precipitated or potentiated by L1-induced redistribution of iron.

We believe that there is reasonable evidence to implicate L1 directly or indirectly in at least three of the four deaths. It is important to make all views public now because of the debate on the future of L1 that is sure to follow the announcement of Ciba-Geigy that further development of the drug is not justified in view of its toxicity (Berdoukas *et al*, 1993), and the subsequent statement from the International Study Group on Oral Iron Chelation that this is premature (Hershko, 1993).

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In developing countries, iron chelation is not available to thalassaemics because of its high cost. Inadequate blood transfusions and splenectomies are common. As a result, most thalassaemics succumb to iron overload or infections during their late second decade. At our centre, analysis of 360 thalassaemics, monitored over 8 years (1983–90), showed cardiac failure and infections including pyogenic meningitis as the main mode of death, which occurred in 52 subjects (Agarwal, 1986).

Four thalassaemic patients on L1, who died during our initial trial, belonged to the age group 15–18 years (Agarwal *et al*, 1992a). Their serum ferritin ranged from 8300 to 12800 ng/ml (Agarwal *et al*, 1992a). All of them were splenectomized and their mode of death was either iron-related cardiac failure or infection and in no way different from thalassaemics dying elsewhere in India.

Mehta *et al* have hypothesized that these deaths may be due to L1-related immuno-paralysis. Their hypothesis is based on animal work carried out by Ciba-Geigy as well as the presence of thymic atrophy in one of our patients who was on L1 (Berdoukas *et al*, 1993).