

## Treatment of Kala-azar in India

Kala-azar disappeared from India in the 1950s, mainly due to the extensive use of DDT under the National Malaria Eradication Programme. However, it reappeared 20 years later causing 4500 deaths<sup>1</sup> among 100 000 cases in 1977. In 1991 there were 250 000 cases in Bihar alone.<sup>2</sup> The disease now affects 30 districts in Bihar, 10 in West Bengal and 2 in Uttar Pradesh.

The objectives of treatment are to cure the malnourished and immunosuppressed patient of the intracellular organism, to prevent a relapse and to prevent the development of resistance to available drugs. It is also essential to minimize the hospital and treatment costs.

Three drugs have been commonly used in the treatment of kala-azar—pentavalent antimonials, pentamidine and amphotericin B. The pentavalent antimonials are the first-line drugs and two of these, sodium stibogluconate and meglumine antimoniate, are available in India and are chemically similar. Their efficacy depends on the pentavalent antimony content which interferes with the metabolic pathways of the leishmanial amastigotes.<sup>3</sup> Meglumine antimoniate solution contains about 85 mg of pentavalent antimony per ml whereas sodium stibogluconate solution contains 100 mg per ml.<sup>4</sup> Common side-effects of these drugs are anorexia, vomiting, nausea, malaise, myalgia, arthralgia, electrocardiographic changes with cardiac arrhythmias and occasionally acute renal failure and death.

The treatment regime for kala-azar varies from country to country. In the 1960s and early 1970s, Indian and Chinese patients suffering from kala-azar were thought to be more sensitive to antimonials than patients in Kenya. Therefore, a 6- to 10-day regime of 10 mg/kg body weight of sodium stibogluconate in a daily intramuscular injection was advocated in India<sup>5</sup> and China<sup>6</sup> whereas a 30-day regime was recommended in Kenya.<sup>7</sup>

In the 1970s, in Bihar, 30% of the patients relapsed and became unresponsive to this dose schedule, while in China the organism remained sensitive till the 1980s. This led to treatment being administered in Bihar for 20 days with a reduction in the unresponsiveness and relapse rates to 7.9% and 0.5% respectively.<sup>8</sup> The World Health Organization recommended that the drug should be given intravenously or intramuscularly in a dose of 20 mg/kg body weight to a maximum of 850 mg/day, for at least 20 days and should be continued for two weeks after anticipated parasitological cure.<sup>4,9</sup> Children tolerate pentavalent antimonials better on a weight-to-weight basis. Patients who relapse after antimonials should be administered the same dose for twice the initial duration.<sup>4</sup>

It was subsequently shown that a 40-day regime was more effective than the 20-day and 30-day regimes.<sup>10</sup> However, the incidence of cardiac toxicity increased when the treatment was extended beyond 30 days due to a cumulative dose effect.<sup>11</sup>

Primary unresponsiveness (defined as no clinical or parasitological improvement during or after the first course of treatment) to pentavalent antimonials was only 8%<sup>4</sup> in the early 1980s and about 25% in 1991.<sup>2</sup> Secondary unresponsiveness occurs after one or more courses of apparently successful treatment and was about 13%<sup>4</sup> (to pentavalent antimonials) in the early 1980s.

Patients not responding to pentavalent antimonials should be administered pentamidine and amphotericin B. Pentamidine, a diamidine, which interferes with the polyamine metabolism of leishmania, is given intramuscularly or intravenously in a dose of 4 mg/kg body weight, thrice weekly, for 5 to 25 weeks.<sup>8,9</sup> In the 1980s only 10 to 15 injections of pentamidine were enough to cure antimony-resistant cases,<sup>1,12</sup> but now 80% of patients require more than 30 injections while in some patients the parasite persists even after 40 injections. It may cause nausea, vomiting, hypoglycaemia or hyperglycaemia, permanent diabetes (as the drug damages islet cells), cardiovascular collapse and sudden death. At a daily dose of 4 mg/kg body weight, a blood level of 0.2 to 0.4 mg/L



persists for at least 24 hours and the drug is excreted slowly in the urine over several weeks. Traces of the drug remain in the kidney, pancreas and liver for months.

Amphotericin B, an antifungal agent which interferes with the lipid metabolism of leishmania, has also been used for the treatment of visceral leishmaniasis in India and Brazil. It is given in a dose of 1 mg/kg body weight starting at 0.05 mg/kg body weight on the first day and increasing the dose daily till the full dose is reached on the fifth day. It is then given on alternate days till a total dose of 1 to 3 g has been administered.<sup>4</sup> It causes rigors and fever with nausea and vomiting on the day of infusion, a rise in blood urea, fall in serum potassium, anaemia and cardiac arrhythmias. It may also be used in patients resistant to both pentavalent antimonials and pentamidine (unpublished data). Used as a first line drug amphotericin B has a 100% cure rate compared to 75% with sodium stibogluconate (personal observation).

Allopurinol, which interferes with purine metabolism, has been found to be effective alone or in combination with antimonials in India<sup>13</sup> and Kenya<sup>14</sup> but I have not found it to be useful.<sup>8</sup> Some other oral drugs including metronidazole,<sup>15</sup> co-trimoxazole,<sup>16</sup> antitubercular drugs<sup>17</sup> and ketoconazole,<sup>18</sup> have been shown to be effective by some workers, but not by others.<sup>19</sup> Recently a liposome preparation, the amphotericin B lipid complex, has been shown to be effective in patients resistant to an antimony and aminosidine combination<sup>20</sup> and is under extensive study in Patna and elsewhere. A combination of pentavalent antimony and interferon gamma has also been used.<sup>21</sup>

The spleen is a reservoir of parasite-laden macrophages and its removal in unresponsive patients has been reported with varying success rates. I have not found splenectomy necessary in any of my patients.

Patients with kala-azar are immunosuppressed and are prone to secondary infections. Diarrhoeal episodes, which may be due to visceral leishmaniasis, should be investigated and treated promptly. Patients with kala-azar are also more prone to develop tuberculosis. Haemorrhagic complications such as epistaxis, haemoptysis and intestinal bleeding due to hypoprothrombinaemia or thrombocytopenia may need blood transfusion. Anaemia is mainly due to bone marrow dysfunction and if severe may also require blood transfusion.

The main problem in the treatment of this recrudescing disease in India is the absence of an effective and cheap oral drug which can be administered with minimum supervision to patients in our villages.

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