Clinicoepidemiological study of drug resistance in Indian kala-azar

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Large scale therapeutic failure of antimony has been the outstanding feature of the current epidemic of Indian kala-azar. Because of the ineffectiveness of a regimen of sodium stibogluconate 10 mg/kg body weight for 6-10 days the World Health Organisation recommended a dosage of 20 mg/kg body weight for 20 days in new cases and for 40 days in relapses.¹ Initial successes achieved with these regimens, however, have not been sustained.^{2,3} Against this background we examined the clinicoepidemiological factors contributing to the unresponsiveness of Indian kala-azar to the drug.

Patients, methods, and results

We studied 312 patients with Indian kala-azar (proved parasitologically) who had received one or more courses of antimony but had failed to recover. The mean weight of these patients was 38.8 (SD 13.3) kg; 169 patients weighed more than 42.5 kg. Only 81 patients had received adequate antimony treatment, according to the WHO's guidelines, before being considered to have refractory disease. Two hundred and twenty seven patients had consulted an unqualified practitioner initially, and 87 of these had consulted one again during their first relapse. Most patients (225) received the drug for less than 40 days; 87 received it for less than 20 days and 147 for less than 30 days. One hundred and thirty two patients did not take it regularly, and 112 stopped taking the drug on their own initiative. Most of them (310) used their own resources to buy the drug. As a consequence of treatment 12 patients developed cellulitis and 13 developed abscesses at the site of injection. The table gives the details of the drug treatment given to patients during their first and second relapses. To our surprise 70 of the 149 patients who received pentamidine during their first relapse had not received adequate antimony treatment.

Comment

Only a quarter of our patients received adequate antimony treatment, while the rest received the drug in subtherapeutic doses before being considered to have refractory disease. In almost three quarters of the cases the drug was not used for the recommended period. The insufficient dosage and duration of antimony treatment may not only be responsible for the patients' lack of response but also help the parasite to develop tolerance and resistance to the drug, thus making a previously highly effective treatment regimen useless.^{2,3} Unqualified practitioners (who are quite unreliable) had treated most of these patients in the study. A considerable number of patients had been given a toxic drug such as pentamidine without being given adequate antimony treatment, and amphotericin B is being used overzealously in India. If such practices continue the parasite may also develop resistance to these drugs, which are currently effective. There are already reports of the parasite developing tolerance to pentamidine.⁴

In India the ceiling of 850 mg antimony recommended by the WHO¹ is strictly adhered to by most doctors. As about half of the patients weighed more than 42.5 kg even strict adherence to the WHO's

criteria would have resulted in their receiving doses lower than 20 mg/kg body weight. Other workers have also questioned the wisdom of this ceiling.⁵ Self withdrawal from the treatment regimen could be ascribed to economic reasons and early amelioration of symptoms as well as patients' poor motivation owing to a lack of knowledge.

Drugs used to treat 312 patients with kala-azar during first and second relapses

Drug	First relapse	Second relapse
Sodium stibogluconate	160	7
Pentamidine	149	52
Ketoconazole	1	1
Amphotericin B	2	
Total	312	60

Given the above facts, obtained from the heartland of the kala-azar epidemic, the therapeutic prospects seem bleak. Most of the affected population, as well as the doctors in the area, are not sufficiently aware of the need for effective treatment and control of kala-azar. This dismal situation also reflects the deficiencies of various training and health education programmes on kala-azar in India during the previous two decades. There is a considerable need and scope for orientation programmes to educate those at risk, doctors, and the government agencies responsible for controlling and preventing kala-azar in India.

- 1 World Health Organisation. The leishmaniasis: report of a WHO expert committee. *WHO Tech Rep Ser* 1984;701:99-109.
- 2 Thakur CP, Kumar M, Pandey AK. Evaluation of efficacy of longer durations of therapy of fresh cases of kala-azar with sodium stibogluconate. *Indian J Med Res* 1991;93:103-10.
- 3 Jha TK, Singh NKP, Jha S. Therapeutic use of sodium stibogluconate in kala-azar from some hyperendemic districts of N Bihar, India [abstract]. *J Assoc Physicians India* 1992;42:868.
- 4 Jha SN, Singh NKP, Jha TK. Changing response to diamidine compounds in cases of kala-azar unresponsive to antimonials. *J Assoc Physicians India* 1991;39:314-6.
- 5 Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg* 1992;46:296-306.

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MEMORABLE TEACHING SESSION

Real help from an unexpected quarter

Finals were two weeks away. After a dispiriting teaching round with an abrasive registrar I fled the ward for the sanctuary of the hospital's back staircase, where, in a flood of tears, I was discovered by two men in overalls.

They put down their buckets and ladders and, squatting down beside me on the steps, gently took a history. The detection and identification of early diastolic murmurs were, they gathered, of major importance. I had failed miserably on both counts and could see no hope of acquiring the required skill by 6 June. Having assessed that, though overwrought, I was not hysterical, one went to find a cup of tea while his colleague explored the problem further. Would the patient mind if I went back and examined her on my own, he asked. Was there anyone else I could approach to teach me? How would I feel about asking a fellow student for help? The cup of tea arrived and they considered with me the likely importance of the bedside interpretation of murmurs firstly to passing my exams and secondly to being a successful general practitioner. Having satisfied themselves that I had adequately regained my composure and had a plan for seeking help, they picked up their equipment and with a final reassuring farewell they went on their way.

I learnt a great deal from the medical school clinicians, even a little cardiology, but I never had a better lesson in the art of the consultation.—JUDITH HARVEY is a general practitioner in Aylesbury