ORIGINAL ARTICLE

Deaths in Visceral Leishmaniasis (Kala-azar) During Treatment

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Summary

Twenty-seven out of five hundred and fifty three patients hospitalized for visceral leishmaniasis (Kala-azar) died during treatment with sodium antimony gluconate. Data from these patients were evaluated to find out the cause of death. Eight patients had associated diseases such as pulmonary tuberculosis (3), severe malnutrition (1), acute gastroenteritis (1), spleenic infarction (1), acute renal failure (1) and atrial septal defect (1) which could be attributed to death. Twelve patients developed spontaneous haemorrhages from nose, gums and gastrointestinal tract and died, despite of adequate supportive measures. Seven other patients who were improving slowly with antimony therapy died unexpectedly. Though, cause of death could be explained in some patients with associated disease conditions, it could not be explained in others as significant clinical manifestations, haematological, biochemical and electrocardiographic alterations were not evident prior to death. Our impression is that mortality in Kala-azar patients during standard antimonial therapy is more related to the drug rather than the disease process.

Key Words: Visceral leishmaniasis, Kala-azar, Antimony, Death

Introduction

There were several epidemics of visceral leishmaniasis or Kala-azar in Bangladesh in the past producing high death tolls[1]. Causes of death in untreated patients were septicaemia, bronchopneumonia, malnutrition and tuberculosis[2]. After the advent of pentavalent antimony for the treatment of Kala-azar, the death rate has reduced dramatically[1]. However, there are several reports of deaths of Kala-azar patients[3-11] (Table I) during treatment with sodium antimony gluconate (SAG) which is a matter of concern for the physicians involved in the treatment of such patients. The cause of such deaths remained unexplained in most cases[5,7]. Recently, there was an outbreak of Kala-azar in Rajshahi (a division of Bangladesh) where we faced a similar problem of deaths in Kala-azar patients during treatment.

The purpose of this communication was to elucidate the causes of death in these Kala-azar patients during treatment with SAG.

Materials and Methods

A total of 553 adult parasitologically confirmed Kala-azar cases of both sexes admitted to the medical units of Rajshahi Medical College Hospital during a period of 30 months were treated with SAG (Stibatin, Glaxo, Bangladesh) at a dose of 20 mg/kg/day (not exceeding 850 mg/day)[13]. Routine blood examination, urine analysis, bleeding and coagulation parameters, hepatic and renal function tests, X-ray chest and electrocardiography (ECG) were done in each case prior to treatment. None had associated hepatic, renal or ischaemic heart diseases. Patients of Kala-azar with tuberculosis received simultaneous antituberculous and SAG therapy. One patient having atrial septal defect (ASD) received the SAG. The drug was continued for 20 days when there were no untoward reactions. Whenever haemorrhagic manifestations in the form of epistaxis, gum bleeding, gastrointestinal (GIT) bleeding, haemoptysis and/or any other untoward manifestation was observed, therapy was immediately stopped, relevant investigations repeated and

supportive treatment given including blood transfusion whenever required. In those cases showing bleeding manifestations after 10 injections, no further injections were given to avoid the risks of further bleeding. When haemorrhagic manifestations occurred before 10 injections, in those who improved with supportive therapy, SAG was restarted either at 10 mg/kg/day or 20 mg/kg/day dose. All patients on 10 mg/kg/day completed the 20 day course without adverse effects. The majority of patients on 20 mg/kg/day experienced bleeding again and the dose had to be reduced to 10 mg/kg/day.

Results

Twenty-seven of of 553 visceral leishmaniasis cases treated with SAG, died. The ages of the 27 (4.9%) patients (17 male, 10 female) ranged from 13-55 years with a mean (± SD) of 26 (± 9.6) years. Among them, 8 had other associated systemic disease conditions (Table II). Sixty seven out of 553 treated patients developed spontaneous bleeding in the form of epistaxis, gum bleeding, GIT bleeding and haemoptysis during therapy. Fifty-five cases improved on stoppage of further SAG therapy and starting supportive treatment including blood transfusion whenever required. Twelve patients died inspite of stoppage of drug and adequate supportive therapy. Prior to death, they became drowsy, toxic and died within a day or two. Strikingly, haemorrhagic manifestations were not severe enough to explain the cause of death. Bleeding and coagulation parameters, liver and kidney function tests and ECG were normal through out the study. Another seven patients who appeared otherwise healthy and were improving satisfactorily with SAG therapy, died unexpectedly although prior to therapy, they had normal renal and hepatic function tests and normal ECGs.

Discussion

Inspite of a correct diagnosis and administration of appropriate therapy, deaths of occasional Kala-azar patients during treatment occur. The death rate varies in different studies due to variations in the patients

Table I
Deaths in Kala-azar patients in different studies during treatment with antiomony

Author(s)	Number of patients treated	Number of patients died	Disease conditions attributable to cause of death
Maru M[3]	18	3	Jaundice and bloody diarrhoea (1), haemorrhagic manifestation (1), sudden death (1)
Aikat BK, *et al.*[4]	813	3	Overwhelming infection (1), pulmonary tuberculosis (1), postpartum haemorrhage (1)
Nasab AH, *et al.*[5]	130	32	Haemorrhagic manifestations (12), bronchopneumonia (10), unexplained death (10)
Thakur CP, *et al.*[6]	692	1	Acute renal failure (1)
Kager PA, *et al.*[7]	64	1	Unexplained shock (1), subdural haematoma (1)
Rees PH, *et al.*[8]	71	5	Generalised bleeding (5)
Bryceson DM, *et al.*[9]	10	1	*Cardiac arrhythmia (1)
Thakur CP[10]	4	3	*Heart failure (3)
Hasan AME, *et al.*[11]	17	2	Haemorrhagic manifestation (2)

Figures within parentheses indicate number of patients
**Very high doses of antimony were used*

Table II
Deaths in Kala-azar patients during treatment with Sodium Antimony Gluconate

Group	Causes of death	No of deaths
I	Attributable to associated diseases Pulmonary tuberculosis (3) Spleenic infarction (1) Severe malnutrition (1) Acute gastroenteritis (1) Acute renal failure (1) and Atrial septal defect (1)	(8)
II	Attributable to haemorrhagic manifestation	(12)
III	Sudden death	(7)

** Figures within parentheses indicate number of patients*

characteristics and differences in the dose schedule[6,9,10]. Overwhelming infection was thought to be responsible for such deaths in some cases given specific therapy[4]. Some of our Kala-azar patients had associated diseases like tuberculosis, gastroenteritis, malnutrition which may have been the contributory factors for their deaths. There are reports of sporadic deaths due to acute renal failure[6] and similar observation was also noted in this study. Death could not be explained in the case of ASD, though cardiac arrhythmia and heart failure have been reported with very high doses of SAG.

A second group of patients had spontaneous haemorrhagic manifestations before death. Bleeding manifestations can also occur in Kala-azar due to the disease process itself and is attributable to thrombocytopenia. Previous studies lend evidence that these haemorrhages were the principal cause for the deaths[3,5,11]. Surprisingly, none of our 553 Kala-azar patients had haemorrhages nor died prior to administration of antimony. It is worth mentioning that on an average, one week is required for investigating such patients before commencing therapy. When therapy was started some of our patients started to bleed either from the nose, gums or GIT. Within a day or two, some patients became drowsy, toxic and died. Those who survived after discontinuation of the drug, in most of the cases, bled again on resuming the therapy at the previous dose[13]. Though, death has been attributed to such bleeding in other studies[3,5,11], our observation is that bleeding was not profuse enough to cause death. Moreover, some patients died inspite of adequate supportive therapy including blood transfusion. Furthermore, bleeding and coagulation parameters, liver and renal function tests did not show any significant abnormality after starting treatment. So, whether death in these cases were simply due to haemorrhage or any other unidentified mechanism, remains to be determined[5]. Perhaps, these deaths are more related to the drug used in the treatment rather than the disease process.

Sudden death in a third group of patients who died unexpectedly during treatment has also been reported by others[3,5]. These patients had no previous associated diseases and were improving satisfactorily with SAG, but suddenly died. Some described these deaths as analogous to the Jarisch-Herxheimer reaction[2], but others were non-committal[3,5]. Though, death due to cardiac arrhythmias[9] or heart failure[10] have been reported earlier with very high dose of antimony, is not certain whether, these sudden deaths could be due to cardiac arrest with the usual dose schedule. Cardiac monitoring in each patient on treatment could have detected the cardiac abnormality prior to death.

Therefore, death of Kala-azar patients during treatment with pentavalent antimonial drug remains a mystery in most of the cases. Whether deaths are due to the relentless course of the disease itself or due to treatment with antimony is still a matter of controversy. Our impression is that the increased haemorrhagic tendencies and unexplained deaths during treatment of our patients is more related to the drug than the disease process itself. Further studies are necessary to determine the cause of death. More importantly, the dose schedule of SAG may have to be reassessed or alternative effective and safe drug may have to be searched for.

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