mazepine was beneficial in controlling tremors resistant to even propranolol therapy.

The mode of action of carbamazepine is because of its structural similarity to phenothiazines(7). The drug blocks at the level of post-synaptic dopaminergic receptors. It also increases the activity of cholinergic system in cerebral hemispheres and corpus striatum which are antagonistic to dopaminergic system. Hence, it has been successfully used in disorders of extrapyramidal system including rheumatic chorea, chorea following head injury and torsion dyntonia(5,6,8).

The clinical features such as tremors and dystonic posture in some infants in ITS suggests involvement of the extrapyramidal system. This prompted us to use carbamazepine therapy for this disorder. The drug is safe with few side effects when given in the recommended anticonvulsant dosages(7). Rash is seen in less than 5% patients and few develop reversible mild leucopenia. Blood dyscrasia and toxic hepatitis are extremely rare.

Carbamazepine was, therefore, effective in controlling tremors in patients with infantile tremor syndrome with no significant side effects. However, accepting the limitation of the study, we recommend further trials with carbamazepine in larger sample of patients before recommending it for routine use in patients with infantile tremor syndrome.

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Amphotericin B in Visceral Leishmaniasis

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Visceral leishmaniasis has assumed epidemic proportions in north Bihar. Pri-

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mary and secondary unresponsiveness have been reported with pentavalent antimony(1-3) as well as pentamidine(4). Second line drugs include ketoconazole, formycin B, sinefungin, aminosidine, gold salts, WR 6026 and co-trimoxazone(5-9). Since there are similarities in the lipid metabolism of leishmania and fungi, amphotericin B a potent antifungal drug is expected to be effective in kala-azar. The drug has shown activity against *Leishmania braziliensis*(10) and inhibits the growth of *Leishmania mexicana amastigotes*(11).

We studied the therapeutic efficacy of amphotericin B in cases with visceral leishmaniasis (kala-azar) unresponsive to the usual drugs.

Material and Methods

Ten patients of visceral leishmaniasis were studied. A diagnosis of visceral leishmaniasis was made on clinical features and presence of Leishman-Donovan bodies (amastigotes) in the splenic aspirate (eight cases) or bone marrow aspirate (two cases). Splenic aspiration was done in all cases in whom the spleen was enlarged more than 2 cm below the costal margin. If splenic enlargement was less than 2 cm below the costal margin bone marrow aspiration was done. Eight patients had previously been treated with sodium stibogluconate in the dosage of 20 mg/kg daily intramuscularly for 30 days. Six cases had failed to respond and two cases had relapsed within 45 days of stopping therapy. Two patients had received pentamidine in a dosage of 4 mg/kg intramuscularly on alternate days for a total of 20 injections. Both these cases relapsed within 60 days after stopping the therapy. Patients of visceral leishmaniasis with associated cardiac, renal, pulmonary or hepatic complications were excluded.

Prior to the therapy, total and differential leucocyte count, the blood levels of hemoglobin, urea, creatinine, sodium, potassium and bilirubin were determined; urine analysis and *X*-ray chest were also done in all cases. Clinical examination included the patients' weight, body temperature, measurement of splenic size (splenic axis in centimetres from the costal margin in anterior axillary line to its tip) and liver size (in mid clavicular line from the costal margin to its margin).

All cases were treated with amphotericin B (Fungizone, Sarabhai Chemicals) containing 50 mg of the drug per vial. Ten ml of sterile water was added to each vial to make amphotericin B solution. A test dose of 1 mg dissolved in 20 ml of 5% dextrose was given slowly intravenously over 30 minutes. If no hypersensitivity was observed, then on next day amphotericin B was given in the dose of 0.2 mg/kg; the dose was stepped up in daily increment of 2.5 mg until the dose of 0.5 mg/kg was achieved. This dose was then administered on alternate days for a total of 21 infusions. The drug was infused dissolved in 250-540 ml of 5% dextrose solution over 4-6 hours.

During therapy patients were clinically examined daily and laboratory investigations were done every week. The criteria for clinical cure were remission of fever, weight gain, regression in splenic size, increase in hemoglobin level and leucocyte count. The criterion for parasitological cure was absence of amastigotes in the splenic or bone marrow aspirate at the end of therapy. Apparent cure was defined as clinical and parasitological cure at the end of therapy. Primary unresponsiveness was defined as no clinical and parasitological improvement at the end of therapy. All patients were followed up at 1, 3, 6 and 12 months after cessation of therapy. During

follow up history was noted, clinical examination, hemoglobin estimation, leucocyte count and urine analysis were done. Aspiration of material for parasites was done in all 10 cases at 3, 6 and 12 months follow-up. Persistence of clinical and parasitological cure at the end of 12 months follow up was defined as full cure. Relapse within a year of stopping the therapy was termed as secondary unresponsiveness.

Results

Tables I & II give data on 10 cases studied. The mean age of patients (7 men, 3 women) at presentation was 7 years (range 2-10). All of these patients were febrile and parasitologically positive. Their mean (SD) splenic size was 6.3(3.6) cm, liver size 2.4(1.6) cm, leucocyte count 2.6 (0.7) $10^9/1$, hemoglobin level 6.8(0.6) g/dl and weight 16.0(6.7) kg.

TABLE I –*Clinical Features During Therapy and Follow-up*

Feature	Before therapy	After infusion		Follow-up (months)			
		10th	21st	1	3	6	12
Fever	10	3	Nil	Nil	Nil	Nil	Nil
Splenomegaly (>2 cm)	8	4	3	2	1	–	–
Amastigote forms							
Splenic aspirate	8(8)	2(4)	0(3)	0(2)	0(1)	–	–
Bone marrow aspirate	2(2)	3(6)	0(7)	–	0(9)	0(10)	0(10)

Figures in parentheses show total number examined.

TABLE II–*Clinical and Laboratory Findings Following Therapy*

Findings	Before therapy Mean ± SD (range)	After therapy Mean ± SD (range)	p value
Weight (kg)	16.0 ± 6.7 (5.0-25.0)	18.0 ± 6.9 (7.0-29.0)	<0.01
Hemoglobin (g/dl)	6.8 ± 0.6 (5.8-7.8)	8.2 ± 0.7 (7.1-9.3)	<0.001
Liver size (cm)	2.4 ± 1.6 (0-4.8)	0.7 ± 0.6 (0-1.4)	<0.01
Splenic size (cm)	6.3 ± 3.6 (1.8-10.6)	1.7 ± 1.3 (0-4.3)	<0.001
Leucocyte count ($10^9/1$)	2.6 ± 0.7 (1.1-3.6)	5.4 ± 1.0 (4.6-7.4)	<0.001
Serum urea (mg/dl)	6.2 ± 1.5 (5.1-10.4)	7.2 ± 1.0 (5.6-8.4)	>0.05
Serum creatining (mg/dl)	0.4 ± 0.1 (0.3-0.6)	0.5 ± 0.06 (0.4-0.6)	>0.05
Serum sodium (meq/l)	139.1 ± 1.8 (138.0-144.0)	140.0 ± 3.0 (137.0-145.0)	>0.05
Serum potassium (meq/l)	3.6 ± 0.2 (3.5-4.2)	3.5 ± 0.3 (3.3-4.3)	>0.05
Serum bilirubin (mg/dl)	0.4 ± 0.1 (0.2-0.7)	0.4 ± (0.3-0.6)	>0.05

p value: <0.01– significant; <0.001–highly significant; >0.05–not significant.

After 20 days of therapy, *i.e.,* after 10th infusion, seven cases were afebrile and five cases parasitologically negative. After 42 days of therapy, *i.e.,* after 21st infusion, all 10 cases were afebrile and parasitologically negative. In all cases splenic and liver size regressed, their mean (SD) fell to 1.7 (1.3) cm and 0.7 (0.6) cm, respectively; leucocyte count, hemoglobin level and weight increased, their mean (SD) rose to 5.4 (1.0) $10^9/1$, 8.2 (0.7) g/dl and 18.0 (6.9) kg respectively. These differences were statistically significant. Primary unresponsiveness was not observed in any case. The only physical finding left over was the presence of parasitologically negative palpable spleens (more than 2 cm below the left costal margin) in 3 cases but interestingly enough that subsided on subsequent follow-up. At follow up after 3 months spleen was not palpable in any case.

Adverse reactions included fever with chill in 8 cases on the day of infusion. This episode usually started within 10-15 minutes of the infusion and was treated easily with intravenous injection of pheniramine maleate; one patient required hydrocortisone. No serious adverse effects necessitating change in blood levels of urea, creatinine, sodium, potassium and bilirubin.

No relapse was noted during one, three, six and twelve months period after cessation of therapy. All cases remained clinically and parasitologically cured at the end of 12 months follow up.

Students 't' test for paired data was used to compare before therapy and after therapy values.

Discussion

In the present study, the dosage schedule used (0.5 mg.kg on alternative days for 21 infusions) was well tolerated by patients. All cases were clinically and parasitologically cured and none relapsed during one year follow-up. Fever with chill was most common adverse effect observed. The capacity of the drug to release interleukin 1 and tumor necrosis factor from human monocytes and murine macrophages is the suggested mechanism of pyrogenicity(10). The drug must be administered in 5% dextrose solution because presence of electrolytes may cause the colloidal suspension to precipitate and result in loss of bioactivity of amphotericin B(12).

Mishra *et al.*(12) used amphotericin B for treatment of patients with kala-azar in the dose schedule of 0.5 mg/kg intravenously on alternative days for a total of 14 infusions. One patient, out of 15 studied, relapsed after 4 months. Amphotericin B has been known to be effective in treatment of visceral(14-16) and mucocutaneous(17) leishmaniasis. However, the dosage schedule is rather high and tends to be toxic. In the present study, the total dose required was lower than used in the New World. A lower dosage, dilution of the drug administered and use of scalp vein needle may have prevented adverse effects.

Amphotericin B is an acceptable second-line drug for treatment of visceral leishmaniasis in children. It may be an alternative to pentamidine which itself is a toxic drug. A formulation containing amphotericin B and liposomes(18) may prove to be more effective and safe. Interferon gamma(19) if combined with amphotericin B may also prove to be useful in management of these cases.

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