Tetany in kala azar patients treated with paromomycin

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Paromomycin, an aminoglycoside, is known to cause several side effects like nephrotoxicity and ototoxicity like other aminoglycosides but tetany has not been reported. Three cases of tetany were detected in the patients of kala-azar treated with paromomycin. They were promptly treated with intravenous 10 per cent calcium gluconate and tetany was relieved immediately and treatment with paromomycin continued with oral calcium supplement. After completion of 21 days treatment with paromomycin patients’ splenic aspirates were free of parasites. Paromomycin may cause temporary tubular damage leading to calcium wasting in urine and hypocalcaemia resulting in tetany. Prompt detection of symptoms and intravenous calcium gluconate treatment promptly reverse the situation.

Key words Intravenous calcium gluconate - kala-azar - paromomycin - pharmacovigilance - tetany

Paromomycin (monomycin, aminosidine) is an aminoglycoside used globally as an antibiotic and antiprotozoal agent; other members of this group are amikacin, gentamycin, kanamycin, netilmicin, streptomycin, tobramycin and apramycin. After demonstration of its anti-leishmanial effect1 paromomycin (PM) has been evaluated as an anti-kala-azar drug in India and Africa2-4. As incidence of kala-azar was increasing in Bihar56 and the efficacy of sodium antimony gluconate, the first line drug in the treatment of kala-azar was decreasing7, there was an urgent need for effective drugs to be used for the treatment of kala-azar.

In a randomized, controlled, unblinded trial with 180 days follow up, paromomycin (aminosidine) at three daily doses (12, 16 and 20 mg/kg/day for 21 days) was compared with sodium stibogluconate (SB) (20 mg/kg for 30 days). Of the 120 patients enrolled (30 per treatment arm), 119 completed treatment and follow up. Cure at the end of follow up was achieved in 23 (77%), 28 (93%), and 29 (97%) patients with 12, 16 and 20 mg aminosidine /kg/day respectively, and in 19 (63%) patients given sodium stibogluconate. It was concluded that 16 and 20 mg/kg/day of aminosidine was significantly more active than sodium stibogluconate in both clinical and laboratory measures of efficacy. No significant clinical and laboratory toxicity occurred in any treatment group8.

In an open label randomized phase II clinical study it was designed to determine the maximum safe and effective dose of paromomycin given at 12, 16 or 20 mg/kg daily for 20 days compared to sodium stibogluconate (20 mg/kg daily, maximum 8.5 ml/day, at 180 days final cure was achieved in 27 of 30, 24 of
27 and 25 of 29 patients given paromomycin 12, 16, and 20 mg/kg daily respectively compared to 20 of 29 treated with SB. Even 12 mg/kg dose of PM was superior to 20 mg/kg of SB and there was no difference between 12, 16 and 20 mg/kg9.

A randomized controlled phase III open-label study comparing paromomycin with amphotericin B, was done in four centres with 667 parasitologically confirmed patients of visceral leishmaniasis who were negative for the human immunodeficiency virus. A total of 502 patients received paromomycin at a dose of 11 mg/kg of the body weight intramuscular (im) daily for 21 days and 165 patients received amphotericin B at the dose of 1 mg/kg intravenously (iv) on alternate days for 30 days in four treatment centres for visceral leishmaniasis in Bihar (Banaras Hindu University, Varanasi, Uttar Pradesh. Kala-azar Research Centre, Brahampura, Muzaffarpur. Bihar, Balaji Utthan Sansthan, Patna and the Rajendra Memorial Research Institute of Medical Sciences, Patna, Bihar)10. Non inferior inferior testing was used to compare 6 months cure rate with a chosen margin of non inferiority 10 percentage points. Paromomycin was shown to be non-inferior to amphotericin B (final cure rate 94.6 vs 98.8%; difference, 4.2 percentage points; upper bound of the 97.5% confidence interval, 6.9; \(P<0.001\)). Adverse events noted in paromomycin group were more common than amphotericin B group (6 vs. 2%, \(P=0.02\)), included transient rise in aspartate aminotransferase levels more than three times the upper limit of normal range, transient reversible ototoxicity (2% vs. 0, \(P=0.20\)), and injection site pain (55% vs. 0). No case of tetany was reported10. As the toxicity of paromomycin was dose related and aggravated by renal failure and use of loop diuretics, these side effects are expected at a high dose11. Because of their potential for ototoxicity and nephrotoxicity aminoglycosides are administered in a dose based on body weight. Vestibular damage, hearing loss, and tinnitus are irreversible, concomitant administration of a cephalosporin may lead to increased risk of nephrotoxicity. Administration of a loop diuretic increases the risk of ototoxicity. Impaired renal function necessitates a reduced dose11. After completion of phase III trials in Bihar, this drug has been registered in India as a drug to be used in kala-azar and is waiting to undergo phase IV trial. Prior to Phase IV trial of this drug, some drugs were provided by IOWH, (Institute for One World Health, USA) to be used in patients (soft launch). During this phase of study, we encountered three cases of tetany caused by paromomycin, no such experience was encountered in any previous studies. We searched world literature on this topic but did not find any mention of this toxicity of paromomycin.

Tetany is usually caused by low ionized serum calcium concentration which causes increased excitability of peripheral nerves resulting in carpo-pedal spasm, convulsion and stridor. The hands in carpo-pedal spasm adopt a characteristic position: metacarpophalangeal joints are flexed and interphalangeal joints of the fingers and thumb are extended and there is an apposition of the thumb and fingers (main’d’ accoucheur). The total serum calcium < 8 mg/dl may be associated with tetany12. We report here three cases of tetany caused by paromomycin treatment in kala-azar patients.

**Case 1:** R K, a 4 yr old female child coming from village Seodaha, an endemic village for kala-azar PS-Dhanaura, District Patna, Bihar came with complaint of fever with chills and distension of abdomen since last 8 days in April 2007. On examination, she was febrile (temperature 38.8°C) and pulse rate was 100/min. Her liver was enlarged 1 cm and spleen 4 cm below costal margin. Her total WBC count was 7,300/µl, Hb 6.4 g/dl, platelet count 1,22,000/µl, ESR-42 mm. ELISA for kala-azar (rk-39) was positive. On splenic aspiration Leish man-Donovan (LD) body 1 (+) was demonstrated. Informed consent was taken from her father.

She was treated with paromomycin injection im (0.3 ml 11mg/kg body weight) daily for 21 days. The patient started improving and her fever subsided. After receiving 13 doses of paromomycin her parents complained of abnormal posture of her both hands after injection. On examination there was carpo-pedal spasm of both hands, metacarpophalangeal joints were flexed with extension of interphalangeal joints of fingers and apposition of thumb. It was diagnosed as tetany and she was given 20 ml of 10 per cent (89 mg of elemental calcium/10 ml) gluconate. She improved well after taking calcium gluconate and paromomycin injection was continued. After completion of 21 days of treatment, her splenic aspirates were negative for LD bodies. Her total serum calcium was 9.6 mg/100 ml. One month after completion of treatment her WBC count was 8.2/µl, Hb 8.2 g/dl, platelet 1,56000/µl, and total serum calcium was 8.4 mg/100 ml. At six months of follow up her splenic aspiration was negative for LD bodies and there was no evidence of hypocalcaemia.

**Case 2:** D K, a 10 yr old male child (Fig. 1) coming from village Ahuara, P.S. Naubatpur, District Patna
came with the complaint of fever for the last two months in April 2007. He was febrile (temperature 37.4°C), pulse rate was 100/min. On abdominal examination his liver was enlarged 1 cm and spleen 4 cm below costal margin.

On laboratory investigation his WBC count was 1700/µl, Hb 4.5 g/dl, platelet count 1,38,000/µl, ELISA for kala-azar (rk-39) was positive. On splenic aspiration, LD body 1(+) was demonstrated.

He was treated with paromomycin injection 0.6 ml i.m. daily, 11 mg/kg body weight for 21 days. After receiving 8 doses of paromomycin his parents complained of abnormal posture of his hands. When the child was given paromomycin, he developed carpopedal spasm of both hands. His total calcium was 6.8 mg/dl. He was diagnosed as a case of tetany and was given 10 ml of 10 per cent calcium gluconate slowly intravenously; Patient improved and paromomycin injection was continued with concurrent use of oral calcium tablets 500 mg once daily. On day 21, his splenic aspirates were negative for LD bodies and he had no signs and symptoms of kala-azar or hypocalcaemia. His total WBC count was 5000/µl, Hb 5.6 g/dl, and platelet count 60,000/µl.

Case 3: N P, a 15 yr old female (Fig. 2) residing in Village Shultanganj, PO Mahendru, District Patna, came with the complain of epigastric pain, with melaena for the last five days and with a history of fever since last one month.

She was already diagnosed as kala-azar patient and was advised miltefosine 100 mg daily for 28 days. After taking thirty capsules of miltefosine 50 mg evening and morning she developed melaena. On clinical examination, she had axillary temperature of 37.4°C, pulse rate 100/min. On abdominal examination, liver was enlarged and spleen was 8 cm. Her total count was 1.200/ml, neutrophil -35 per cent, lymphocyte - 62 per cent, basophil - 0.1 per cent, monocyte - 0.5 per cent, eosinophil - 0 per cent, haemoglobin - 6.4 g/dl, platelet count- 6.2,000/µl, her body weight was 45 kg. Her splenic aspirates showed (2+) LD body.

She was given 300 ml of blood transfusion daily for three consecutive days and two units of platelet transfusion; 2 ml of dexamethasone was given every 6 h. Bleeding stopped after 2 days. On day 24, she developed tetany. Her total serum calcium was 6.1 mg/dl. She was treated with calcium gluconate 10 per cent (equivalent to 9 mg of elemental. Calcium) for 3 days and then orally 50 mg tablet one tablet thrice daily. She had no recurrence of symptoms.

Splenic aspiration done after 21 days of treatment did not show any LD body. Her spleen and liver size reduced to 1 cm and 0.5 cm respectively. One month after completion of treatment, her total WBC count was 5.200/µl, neutrophil 64 per cent, lymphocyte 30 per cent, basophil 5 per cent, monocyte 1 per cent. At six months of follow up she was free from kala-azar or tetany.

In 17 yr of experience with this drug in India when we started trial of this drug in early1990s, we did not come across a single case of tetany till 2006. All the
three patients might have previous low serum calcium aggravated by paromomycin or paromomycin might have caused hypocalcaemia and tetany. Unfortunately serum calcium of patients prior to starting treatment were not available.

The phase III trial of paromomycin was done at four centres in Bihar10, nowhere it occurred in phase II and III trials. The inclusion criteria for patients for those trials were very strict and exclusion of many poor patients who had either otitis media, anaemia or other conditions which are commonly present in the poor patients, might have been the cause for non occurrence of tetany. However, when the drug was used for all unselected patients of kala azar, as we did in this study similar situation might arise in future. It has been seen that even in healthy subjects gentamycin caused temporary tubular damage, loss of calcium, magnesium and potassium in urine resulting in hypomagnesaemia, hypocalcaemia and hypokalaemia. This phenomenon has been attributed to aminoglycoside induced distal convoluted tubular injury13. Hypomagnesaemic hypocalcaemia secondary to renal magnesium wasting occurred when large doses of gentamicin was given14. Aminoglycosides and vancomycin when administered together in low birth weight infants caused renal tubular wasting of potassium, phosphate, and calcium, along with hypokalaemia but renal effect was temporary15. In preterm neonates gentamycin given for suspected infection caused loss of microalbumin in urine, and loss of sodium and calcium16.

This phenomenon has also been observed in critically ill patients when vancomycin and gentamycin were used together17. In dairy cows parental administration of aminoglycoside reduced blood calcium concentration. Gentamycin was tested in vitro in blood drawn from cows, dihydrostreptomycin was tested in nonlactating cows and neomycin was tested in post partum cows. The total and bound calcium fractions were significantly reduced by all three antibiotics18. Hypomagnesaemic tetany associated with prolonged treatment with aminoglycoside has been reported19 possibly due to excessive accumulation of aminolycolyside in the kidney, 40 per cent of total body gentamycin20 and also with the use of repeated courses of intravenous tobramycin in a patient with cystic fibrosis21. Amphotericin B administration might cause hypomagnesaemic tetany relieved only by magnesium administration22. In all the three patients reported here calcium gluconate relieved tetany. Magnesium supplementation was not required. It is possible that paromomycin belonging to the group of aminoglycoside might have caused hypocalcaemia by the same mechanism of tubular injury. In case 3 tetany occurred three days after completion of the course of treatment, it meant renal tubular injury persisted for some time as reported earlier22.

A detailed study of calcium metabolism after paromomycin administration is needed. Paromomycin like other antibiotics of this group may cause renal loss of calcium resulting in hypocalcaemia and tetany. Intravenous calcium gluconate reverses this condition immediately and the treatment with paromomycin can be continued with oral calcium supplementation.

References


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