**Abstract**

Ifosfamide, a commonly used chemotherapeutic agent in various regimens for many malignancies and has a well known central nervous system side effect. Ifosfamide induced encephalopathy develops in approximately 10-30% of patients exposed to the drug. It is generally reversible after discontinuing the therapy; however cases of fatal neurotoxicity have been reported in literature. Commonly used antidote, Methylene blue; has a moderate efficacy in reversing the encephalopathy followed by lesser response rates by Thiamine. We submit a case report of a young female patient with refractory diffuse large B cell lymphoma who developed severe ifosfamide neurotoxicity. With the use of intravenous thiamine, encephalopathy resolved in our patient within a mean time of 30 hours (average range is 10-30 hours). We found Thiamine to be safe and effective in treatment for ifosfamide induced encephalopathy.

**Introduction**

Ifosfamide is an alkylating chemotherapeutic agent used in various chemotherapy regimens to treat germ cell tumors, sarcomas and lymphomas and other solid organ malignancies. Its common side effects include nausea, vomiting, myelosuppression, haemorrhagic cystitis, interstitial pneumonitis, arrhythmias and alopecia. Encephalopathy is also a well-known side effect and it develops in approximately 10-30% of patients exposed to it. Common symptoms of encephalopathy include confusion, disorientation, hallucinations, psychosis, diplopia, asterixis, dysarthria, muscle spasticity, extrapyramidal symptoms, seizures and coma. The neurological toxicities can be graded from 0 to 4 according to the national cancer institute toxicity grading for encephalopathy. There is no established dose-toxicity relationship and neither is there any relationship between the development of neurotoxicity and rate of ifosfamide infusion. Encephalopathy develops usually within 2-48 hours of ifosfamide infusion but rarely may occur several days after the infusion. It is generally reversible within 1 to 3 days after discontinuing the therapy, however cases of fatal neurotoxicity like organic brain damage, coma and death have been reported.

Several mechanisms for the etiology of ifosfamide-induced neurotoxicity have been described and most center on a metabolite of ifosfamide, Chloracetaldehyde. Ifosfamide is metabolized in the liver by the cytochrome P-450 enzyme to active moiety ifosforamide mustard, which acts as an alkylating agent. Several other metabolites are formed in the multistep process. Chloroethylamine (another metabolite) conjugates with cystein forming thialysine, which can be metabolised to thialysine ketimine. The latter can inhibit electron-binding flavoproteins in the mitochondrial respiratory chain, leading to inhibition of mitochondrial respiration and accumulation of Nicotinamide adenine dinucleotide (NADH). This NADH accumulation, in turn, prevents the dehydrogenation of ifosfamide metabolite chloracetaldehyde and hence its accumulation. Chloracetaldehyde can cross the blood-brain barrier. It is structurally similar to neurotoxic metabolites of ethanol and chloral hydrate and may exert inhibitory effects on the CNS.

Methylene blue has been frequently used in the treatment of ifosfamide induced encephalopathy. It acts as an electron-accepting agent, thereby preventing the derangement of mitochondrial metabolism caused by chloracetaldehyde. Also there is evidence that supports the clinical efficacy of thiamine in reversing ifosfamide encephalopathy. Thiamine is phosphorylated to thiamine Pyrophosphate (TPP), its active form, which acts as a coenzyme for oxidative decarboxylation and in transketolase reactions. Thiamine deficiency leads to reduced TPP availability with failure in ATP synthesis and abnormal carbohydrate metabolism, causing altered cerebral energy metabolism. It is now known that Ifosfamide and/or its metabolites compete with TPP function. An exogenous thiamine supply could displace the equilibrium in favour of the phosphorylated forms and hence restore the normal cerebral functions.

**Case Report**

A 32 year married female came to medical oncology outpatient department in January 2009 with three months history of backache, abdominal pain, fever, drenching night sweats, loss of appetite and loss of weight. She had history of right sided hemicolectomy a month earlier for an ileocecal mass visualized on CT scan. The histopathology confirmed a diffuse large B cell lymphoma (DLBCL). She was clinically staged as II E B. After 4 cycles of standard chemotherapy regimen, CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone), in April 2009 she was found to...
have progressive abdominal nodal disease. A repeat biopsy of the abdominal mass again confirmed DLBCL and she was offered second line chemotherapy. There was no clinical or radiological response in her disease after 4 cycles of RDHAP (Rituximab, Dexamethasone, Cytarabine and Cisplatin) regimen. She developed mild biochemical renal dysfunction, primarily cisplatin induced and partly due to a prolonged diarrheal illness causing a prerenal insult. On 6th August 2009 she was admitted to inpatients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 for third line chemotherapy, ICE (Ifosfamide, Carboplatin, Etoposide) with 25% reduced dose of Etoposide as her serum creatinine was 1.54 mg/min and calculated Creatinine clearance (CrCl) was 50ml/min. On third day of her chemotherapy when she had finished her 24 hour infusion of Ifosfamide and Mesna and the post ifosfamide Mesna was on flow she was reported to be drowsy. Her vitals were stable, urine out put was adequate, pupils were dilated but responsive to light, she had generalized increased tone of her body with brisk deep tendon reflexes and Babinski’s sign positive bilaterally. There was no papilloedema on fundoscopy and her Glasgow coma scale (GCS) rapidly deteriorated from 9/15 to 3/15 over the next three to four hours. Her arterial blood gases (ABG’s) showed compensated metabolic acidosis and electrocardiogram (ECG) revealed a left axis deviation with sinus tachycardia. Her blood work up including complete blood counts, urea and electrolytes, serum calcium, magnesium and phosphorus were all within normal range. Her narcotic pain medications (morphine sulphate tablet 30mg bid) and antiemetics (metoclopramide, ondansetron and decadron) were withdrawn and a neurology opinion was sought and she was shifted to intensive care unit. The differential diagnosis included meningoeencephalitis/ space occupying lesion/drug induced encephalitis (Ifosfamide neurotoxicity). An MRI brain was requested urgently which was reported normal. She was started on menengitic dose of Ceftriaxone and Methyl Predisolone 1gm IV OD after sending her blood and urine cultures. Diagnostic lumbar puncture was carried out and the cerebro spinal fluid (CSF) examination revealed normal cell count, biochemistry and cytology. Thereafter, (within 6 hours of her mental deterioration) strongly suspecting Ifosfamide neurotoxicity she was started on Methylene Blue 50mg in 250ml of Dextrose water (D5W) IV q 6hrly. After 36 hours of no improvement in patients neurological score methylene blue and methylprednisolone were discontinued and she was started Thiamine 100mg in 100ml Normal Saline (NS) IV q 4hrly. Patient developed a tonic clonic seizure and was loaded with Phenytoin at the same time. After seven doses of Thiamine patient started to response and her GCS improved dramatically to 13/15. Thiamine was continued for a total of 72 hours. Patient became fully conscious, awake, hemodynamically stable and fully ambulatory. Patient's serum creatinine went up to 3mg/dl on day 6 of her chemotherapy during the course of encephalopathy but she maintained a normal urinary output through out. This is a remarkable recovery seen from ifosfamide toxicity by thiamine at our institution.

**Discussion**

Ifosfamide induced encephalopathy is not too rare side effect of ifosfamide and here we report a case that dramatically responded to Thiamine after failing methylene blue.

Serum electrolytes should always be assayed in all patients with neurological disorders during treatment with ifosfamide. We, in our patient ruled out the possible correctable electrolyte imbalances and kept the patient well hydrated and maintained a good urine output despite a moderately low creatinine clearance.

The objective of radiological examination of brain in such patients is to exclude cerebral haemorrhage, infection or metastasis. Electroencephalography (EEG) is consistent with changes of metabolic encephalopathy. We reported a normal MIR brain in our patient.

There are certain risk factors for the development of ifosfamide induced encephalopathy which include low serum albumin levels, hyponatraemia, elevated serum creatinine, previous cisplatin use, poor performance status, female sex, elderly age and bulky abdominal/pelvic disease. Our patient had an altered serum creatinine level with major disease bulk in her pelvis and a previous history of cisplatin use.

Although, anecdotally, methylene blue is reported to be extremely effective in reversing ifosfamide induced encephalopathy. To date no controlled clinical trials have been carried out to validate these findings. In a recent review by Patel et al, a modest efficacy of methylene blue has been reported. This along with its potential side effects like nausea, abdominal pain, dizziness, headache, profuse sweating, methaemoglobinemia, hypertension, arrhythmias and haemolytic anaemia underscores the need for finding a better, safer and more efficacious alternative to prevent and treat ifosfamide induced encephalopathy. Buesa et al in their case series reported a dramatic improvement in ifosfamide induced encephalopathy with thiamine.

Here, we report the utility of thiamine in our patient with ifosfamide induced encephalopathy who did not respond to treatment with methylene blue. On the basis of the clinical efficacy demonstrated by thiamine in reversing ifosfamide encephalopathy, we support the hypothesis that ifosfamide and/or its metabolites such as Chloracetaldehyde interfere with thiamine function. This explains the similarities between neurological symptoms in patients with ifosfamide...
encephalopathy and those of Wernicke's encephalopathy provoked by severe thiamine deficiency. Our patient developed grade 4 central nervous system neurotoxicity and recovered remarkably with in 30 hours of thiamine use. Thiamine has a safe toxicity profile; common side effects are local irritation, itching, sweating and nausea.

We propose that risk factors and metabolic derangements in patients receiving ifosfamide be promptly identified and corrected. For patients who develop CNS symptoms suggestive of ifosfamide encephalopathy we should keep a high suspicion of index and start treatment with thiamine without delay. Thiamine appears to be safe and effective in treatment of ifosfamide induced encephalopathy although larger studies are needed to confirm our observation.

References