CASE REPORT
Role of thiamine in managing ifosfamide-induced encephalopathy

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Sir – Ifosfamide, a structural analog of cyclophosphamide, is an alkylating chemotherapeutic agent. It is used extensively in different chemotherapy regimens to treat various malignancies, including lymphomas, sarcomas, testicular tumor, cervical cancer, Ewing’s sarcoma, osteogenic sarcoma, and head and neck cancer. Common adverse effects include nausea, vomiting, myelosuppression, hemorrhagic cystitis, interstitial pneumonitis, arrhythmias and alopecia. Encephalopathy is a well-known side effect of ifosfamide,1 developing 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. Methylene blue is commonly used in the treatment and prophylaxis of ifosfamide induced encephalopathy; however, its efficacy is moderate at best. We report here the utility of thiamine in both treating and preventing ifosfamide induced neurotoxicity in three patients. With the use of intravenous thiamine encephalopathy resolved in all of our patients within a mean time of 17 hours (range 10–30 hours). In three cycles where thiamine was used as prophylaxis no evidence of ifosfamide induced encephalopathy was seen. Thiamine appears to be a safe and effective treatment for reversing encephalopathy resulting from ifosfamide infusion, without any significant side effects. J Oncol Pharm Practice (2006) 12: 237–239.

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neurotoxic substance. Risk factors for the development of IIE include, low serum albumin (<3.5 g/dL), elevated serum creatinine, previous cisplatin use (>300 mg/m² cumulative dose), prior nephrectomy, poor performance status, and history of ifosfamide-induced neurotoxicity.4,5

Methylene blue is commonly used in the treatment and prophylaxis of IIE. It has been proposed that methylene blue acts as an electron accepting agent, thereby correcting derangement in mitochondrial flavoproteins. It prevents encephalopathy by a different mechanism when used prophylactically, namely oxidation of excessive NADH formed during ifosfamide metabolism.6 Although, anecdotally, methylene blue is reported to be extremely effective in reversing IIE, to date, no controlled, clinical trials have been carried out to validate this report. In a recent systematic review of the literature, Patel et al.,7 reported only a modest efficacy of methylene blue in most patients. This finding, combined with the possible side effects of methylene blue, including nausea, abdominal and precordial pain, dizziness, headache, profuse sweating, mental confusion, methemoglobinemia, etc., underscores the need for finding better, safer and more efficacious alternatives to prevent and treat IIE. Buesa et al., reported a dramatic improvement in IIE with thiamine.8 Here, we report the utility of thiamine in both treating and preventing ifosfamide-induced neurotoxicity in three patients. We used the National Cancer Institute’s common toxicity criteria (version 2.0) to assess the severity of IIE.

Case 1
A 33-year-old Caucasian male with metastatic chondroblastic osteosarcoma was admitted to undergo a third cycle of chemotherapy with high dose ifosfamide (2800 mg/m² per day for five doses iv) and doxorubicin (25 mg/m² per day for three doses iv) in the adjuvant setting. His second cycle of chemotherapy was complicated by the development of IIE. During the third cycle, the patient was given prophylaxis against IIE with methylene blue (50 mg iv every 8 hours). On day four of chemotherapy, the patient developed confusion, disorientation and somnolent. There was no clinical or laboratory evidence of metabolic or infectious problems leading to altered level of consciousness. Ifosfamide was discontinued, and methylene blue was increased to 50 mg iv every 6 hours. On day five (36 hours after stopping ifosfamide), the patient deteriorated neurologically, developing tremors and became less coherent (grade III neurotoxicity). At this point, based on the report of Buesa et al.,8 we started the patient on 100 mg of thiamine iv every 4 hours, and methylene blue was discontinued. A marked improvement in the patient’s neurological symptoms was noted within 10 hours of starting thiamine. The patient fully regained his baseline neurological status. Encouraged by this finding, we used thiamine (100 mg iv every 4 hours) as prophylaxis during the fourth cycle of chemotherapy. The patient tolerated his fourth cycle of chemotherapy (no dose reduction of ifosfamide was carried out) without any signs of IIE.

Case 2
A 51-year-old Caucasian female with newly diagnosed metastatic high grade soft tissue sarcoma was admitted for a first cycle of chemotherapy with high dose ifosfamide (2500 mg/m² per day for four doses iv) and doxorubicin (25 mg/m² per day for three doses iv). The patient had normal renal function, normal serum albumin, and no history of cisplatin use in the past, or encephalopathy. The patient tolerated the chemotherapy without any side effects during the first 2 days; however, during the third dose of ifosfamide, she started experiencing visual and auditory hallucinations, agitation and tremors (grade III neurotoxicity). Ifosfamide infusion was stopped and the patient was started on thiamine (100 mg iv every 4 hours). The patient’s neurological examination was completely normal 12 hours after starting thiamine. Thiamine was used prophylactically during the next two cycles of chemotherapy (no dose reduction of ifosfamide) without any manifestations of IIE.

Case 3
A 66-year-old Caucasian male with a history of prostate cancer treated with pelvic radiation (7000 cGy), presented with newly diagnosed metastatic pelvic pleomorphic sarcoma. His baseline chemistries and renal function were within normal limits. Chemotherapy with ifosfamide (2500 mg/m² per day for three doses iv) and doxorubicin (20 mg/m² per day for three doses iv) with neoadjuvant intent was started. Six hours before completion of the last infusion of ifosfamide, the patient developed confusion, delirium and agitation (grade II encephalopathy). Infectious, metabolic and organ causes were
ruled out. Ifosfamide was stopped, and the patient was started on intravenous thiamine, which resulted in resolution of encephalopathy in 30 hours after the first thiamine dose. Patient declined further chemotherapy or surgery.

In summary, IIE resolved in all of our patient within a mean time of 17 hours (range: 10–30 hours) from the beginning of thiamine administration. In three cycles, where thiamine was used as prophylaxis, no evidence of IIE was observed. This is important, since previously, IIE was a risk factor for further neurotoxicity with additional infusions of ifosfamide. Thiamine’s side effects are uncommon and include local irritation, itching, sweating and nausea. None of our patients developed any untoward events. Our study provides further evidence of thiamine’s efficacy in reversing IIE. Although head to head comparison between methylene blue and thiamine in treating IIE is unlikely to be performed, we did notice reversal of ifosfamide toxicity in a patient not responding to methylene blue (Case 1). Further larger studies are needed to confirm our observation. In conclusion, thiamine appears to be a safe and effective agent to prevent and treat IIE.

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REFERENCES