

## Case of fosphenytoin induced acute cerebellar dysfunction and pituitary bleed causing central diabetes insipidus in a case of AML M2 during allogenic hematopoietic stem cell transplant

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### ABSTRACT

Neuroprotectors such as phenytoin, fosphenytoin, clonazepam or levetiracetam are often used prior conditioning regimen to prevent seizures caused due to busulfan, during bone marrow transplant. Fosphenytoin and levetiracetam are used instead of phenytoin as they are readily soluble and do not need a vehicle such as polyethylene glycol or ethanol which increases risk of tissue and cardio toxicity. We report a case of acute toxicity in the form of cerebral bleed during intravenous administration of fosphenytoin and its subsequent management in patient undergoing busulfan treatment prior to allogenic transplant.

**Key words:** Neuroprotector, phenytoin, fosphenytoin, levetiracetam, bone marrow transplantation, conditioning regimen, busulfan.

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### INTRODUCTION

Fosphenytoin is a phenytoin prodrug that is quickly and completely converted to phenytoin after intravenous or intramuscular administration.<sup>[1]</sup> Busulfan has been regularly used in conditioning stem cell transplantation (SCT) for nearly 20 years.<sup>[2]</sup> Neuroprotectors are used to prevent the neurotoxicity associated with busulfan conditioning regimen. However, neuroprotectors such as phenytoin which are used with a solvent polyethylene glycol can cause tissue necrosis and cardio toxicity. So far an antiepileptic drug - induced encephalopathy (ADE) was reported under the use of phenytoin.<sup>[3]</sup> Psychosis is also a recognized manifestation of phenytoin toxicity.<sup>[4]</sup> The adverse effects seen with use of phenytoin are usually circumvented by use of fosphenytoin. However, in this case we present a patient who developed acute cerebellar dysfunction with pituitary stalk bleed leading to diabetes insipidus following the administration of neuroprotector fosphenytoin,

prior to his conditioning regimen with busulfan. The patient was then managed for central diabetes insipidus followed by conditioning regimen and the peripheral blood stem cells (PBSC) transplant.

### CASE REPORT

A middle aged male patient was diagnosed with acute myeloid leukemia (AML M2) in August 2011. A Bone marrow biopsy revealed hypercellular packed marrow showing sheets of blasts (90%). Normal marrow elements were suppressed and megakaryocytes were not seen. Post his clinical profiling and relevant lab investigations, he was started with induction chemotherapy with

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daunorubicin 60 mg/m<sup>2</sup>/day for three days and cytarabine 200 mg/m<sup>2</sup>/day for seven days. Patient attained cytological remission (CR). He was advised upfront allogenic bone marrow transplantation. He did not opt for the bone marrow transplantation and was initiated on re-intensification chemotherapy on high dose cytarabine consolidation 3 gm/m<sup>2</sup>/day for three days. He was then planned for allogenic PBSC transplantation and patient's brother was found to be an 8/8 allelic HLA antigen match. A PBSC harvest was obtained from the brother, which generated 30 x 10<sup>6</sup> cells/kg of total CD34 cell count.

The patient was put on a conditioning regimen prior to the transplantation. He was initiated on prophylactic anti-epileptic fosphenytoin, prior to busulfan conditioning therapy. 100 ml of aqueous solution containing fosphenytoin in dose of 15 mg/kg body weight (9.6 mgm/mL) was infused intravenously. Approximately 20 minutes into infusion with over 70 mL of the solution being infused, patient developed acute cerebellar dysfunction as evidenced by bilateral in-coordination, pendular nystagmus, cerebellar dysarthria and postural hypotension. Infusion was stopped immediately. Fundoscopy revealed new onset left paramacular bleed. MRI scan of the brain (Figure 1) showed bleed in the neurohypophysis extending to the stalk. The neuroparenchyma was unremarkable.

The patient went into polyuria. Work up was consistent with central diabetes insipidus. The cerebellar deficits intensified over day two. Patient regained co-ordination followed by normal speech with some residual slurring by day three. The pendular nystagmus ceased slowly over the next three days. Postural hypotension was managed as per standard care. The paramacular bleed resolved spontaneously over the next one week. Diabetes insipidus was managed with

**Figure 1: MRI scan of the brain MRI scan of the brain showed bleed in the neurohypophysis extending to the stalk**



treatment for dyselectrolytemia and volume resuscitation with appropriate steroids replacement was done. Desmopressin was not initiated as osmolarity improved with the above measures. Transplant was delayed till normalization of the biochemical parameters, normalization of vision and regression of the pituitary bleed.

A month later a review MRI showed regression in the pituitary bleed. The patient had a stable condition and was initiated on conditioning regimen, which consisted of Inj. busulfan for four days (0.8 mg/kg/dose), followed by Inj. cyclophosphamide (60 mg/kg/day). This was done with adequate hydration and Inj. levitriacetam (500 mg/twice daily) as a neuroprotector (instead of fosphenytoin) which was tolerated well. The collected PBSC from the donor was infused and prophylactic antifungal, antiviral and prophylaxis for *Pneumocystis jiroveci* was continued. The patient did not have

any signs of acute graft versus host disease post-re-infusion and he was maintained on methotrexate and cyclosporine A based immunosuppression. He engrafted on Day 12.

Chimerism study on day 100 showed 100% donor cells. Patient had no repeat events or long term cerebellar deficits related morbidity.

## DISCUSSION

Phenytoin is a preferred drug in the management status epileptics<sup>[5]</sup> but it has two main disadvantages. First, it cannot be administered intramuscularly (IM) due to precipitation at the site of injection, thus causing delay in absorption and tissue necrosis.<sup>[6]</sup> Rapid intravenous (IV) administration is related with the increase of cardiovascular side-effects such as hypotension which requires personal monitoring of the patient. Fosphenytoin is chemically known as 5, 5-diphenyl-3-[(phosphonoxy) methyl]-2, 4-imidazolidinedione disodium salt. The pharmacokinetic profile of fosphenytoin has been investigated in randomized trials in healthy volunteers<sup>[6]</sup> and patients with epilepsy. The bioavailability of phenytoin derived from fosphenytoin given by intravenous or intramuscular injection is approximately 100%.<sup>[5,6]</sup> Intravenous fosphenytoin is rapidly metabolized (10 to 21 minutes) and completely converted to phenytoin and is independent of dose and rate of administration.<sup>[7,8]</sup> As a result of concentration dependent protein binding, intravenous fosphenytoin and phenytoin are bioequivalent when administered at the recommended

infusion rates of 100 to 150 mg phenytoin equivalents/min and 50 mg/min, respectively.<sup>[7,8]</sup>

Fosphenytoin also binds well (93-98%) to plasma proteins. Saturable binding at higher plasma concentrations results in an increased distribution volume and clearance with increased doses and infusion rate. Close supervision and reduction in the infusion rate by 25 to 50% are recommended when IV doses of fosphenytoin are administered in these patients.<sup>[7,8]</sup>

Levetiracetam is a more recently certified anti-epileptic drug (AED) which is being used in different epileptic syndromes including status epilepticus.<sup>[9]</sup> The nonexistence of hepatic metabolism and protein binding predict lack of pharmacokinetic interactions of levetiracetam with other protein binding drugs. Therefore, no clinically important pharmacokinetic interactions of levetiracetam with other AEDS or with other commonly approved medications in critical care settings have been reported.<sup>[10]</sup> Levetiracetam could be a prospective neuroprotector in conditioning regimen before BMT.

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