Treatment of Ifosfamide Encephalopathy with Intravenous Thiamin

Encephalopathy is a well-known side effect of IFOS. This syndrome develops in ~10% of patients exposed to the drug and usually disappears after stopping therapy, although some patients may die without recovery (1). It has been proposed that IFOS metabolites may interfere with the function of flavoproteins, leading to the observed CNS disturbances (2), and therapy with methylene blue has been successfully applied to reverse this unfavorable event (3). On the other hand, oxidation of IFOS lateral chains generates CAA, a metabolite similar to ethanol or chloral hydrate that, as well as these, might diffuse into CNS and cause toxicity. High CAA levels have been detected both in patients with or without IFOS neurotoxicity, and therefore, the CAA role in this syndrome is not well established (1, 4, 5). In our center, the neuropathological study of a woman dying of IFOS neurotoxicity (8), confusion (8), hallucinations (5), anxiety (3), or asterixis (3). In seven cycles, signs of encephalopathy were noted before completing IFOS therapy, which was interrupted in 6 patients. All 10 patients fully recovered after a median time of 36 h (range, 8–72 h) from the beginning of thiamin infusion, and in some, we noticed a close temporal relationship between this treatment and reversal of symptoms. For instance, confusion, depressed levels of consciousness, and anxiety in patients 4 and 5 resolved within 8 h after start of thiamin, although complete recovery occurred later; patient 8 was oriented 5 h after the first dose of thiamin, and asterixis, somnolence, and disphasia disappeared in 30 min in patient 6. In our patients, median time to recovery from CNS toxicity was very similar to the 12–72-h time period reported for patients treated with methylene blue (3), and none required this product to reverse encephalopathy.

Our experience with prophylactic use of thiamin is limited to patients 1, 5, and 10 who received additional IFOS cycles without presenting new episodes of CNS toxicity. In those cycles, thiamin was delivered either i.v. (100 mg every 6 h) or p.o. (300 mg every 12 h) concomitantly with IFOS infusion.

We obtained some information on thiamin levels in patients exposed to IFOS. A blood sample was collected before the start of IFOS infusion and in the last day of the cycle, and total free thiamin content in whole blood was quantified by high-performance liquid chromatography (7). Normal values for this determination range between 2 and 7.2 μg/dl. Thiamin levels (mean ± SD) before and after therapy were 6.10 ± 1.36 and 5.41 ± 1.35 μg/dl, respectively, in 11 patients without CNS toxicity (paired comparison of means, P = 0.21), and 5.22 ± 0.90 and 4.15 ± 1.14 μg/dl in 3 women (four cycles) with CNS toxicity (Wilcoxon signed ranks test for paired samples, P = 0.068).

On the basis of the clinical efficacy demonstrated by thiamin in reversing IFOS encephalopathy, our hypothesis is that this drug and/or its metabolites such as CAA may interfere with thiamin function. This would explain the similarities between CNS symptoms in patients treated with IFOS and those of Wernicke’s encephalopathy provoked by severe thiamin deficiency, often associated with alcoholism. Ingested thiamin is phosphorylated to TPP and TTP, its active forms. TPP acts as a coenzyme for oxidative decarboxylation of α-keto acids and in transketolase reaction. Thiamin deficiency leads to reduced TPP availability with failure in ATP synthesis and abnormal carbohydrate metabolism, causing altered cerebral energy metabolism. Also, TTP has been implicated in the function of membranes and in nerve conduction (8). When recognized, i.v. administration of thiamin reverses Wernicke’s encephalopathy, a syndrome that, otherwise, would cause the death of the patient (6, 8).

Phosphorylated thiamin is transported by RBCs, where 80% of total blood thiamin is present as TPP and 10% as TTP; small amounts of free thiamin and thiamin monophosphate are detected in plasma (8). Our data on thiamin levels in whole blood from patients without CNS toxicity are limited but suggest that thiamin concentration would not change significantly during IFOS therapy. The information obtained in only four cycles with neurotoxicity precludes us for advancing any conclusion. The analytical method applied, which included RBC lysis and enzymatic dephosphorylation of thiamin, quantified total thiamin content and did not allow to detect alterations in the pattern of thiamin phosphorylation, eventually induced by IFOS and leading, for instance, to decreased TPP availability. Alternatively, IFOS and/or its metabolites could compete with TPP or TTP function without necessarily reducing thiamin...
availability, and an excess of thiamin supply could displace the equilibrium in favor of the phosphorylated forms, restoring the normal function of enzymes dependent on TPP or TTP. A genetic sensitivity to thiamin deficiency, as has been described in patients suffering from Wernicke’s encephalopathy, could mediate this IFOS toxicity (9). Additional work is in progress to clarify those hypothesis.

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References

Table 1  Evolution of IFOS neurotoxicity after treatment with i.v. thiamin

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* Grade of neurotoxicity/cycle according to National Cancer Institute Common Toxicity Criteria scale (version 2.0, March 1998).
† Hours elapsed from first thiamin dose to complete disappearance of symptoms.
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