Hospital Pharmacy
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# Successful treatment and prevention of cisplatin-/etoposide-induced encephalopathy with thiamine

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## Background

Cytostatic drugs, that typically may cause encephalopathy comprise methotrexate and ifosfamide. Ifosfamide-induced encephalopathy occurs in 10 to 40% of the patients receiving high-dose ifosfamide and can be successfully treated and prevented with either methylene blue and/or thiamine.

For cisplatin, neurotoxicity is a common adverse effect, mainly limited to axonal sensory neuropathy, however central nervous system disorders have also been reported. Etoposide is highly protein-bound and poorly penetrates to the central nervous system. CNS toxicity is very rare when used at conventional doses. Occasionally, headache, seizures or encephalopathy can occur after (high-dose) etoposide

## Case description

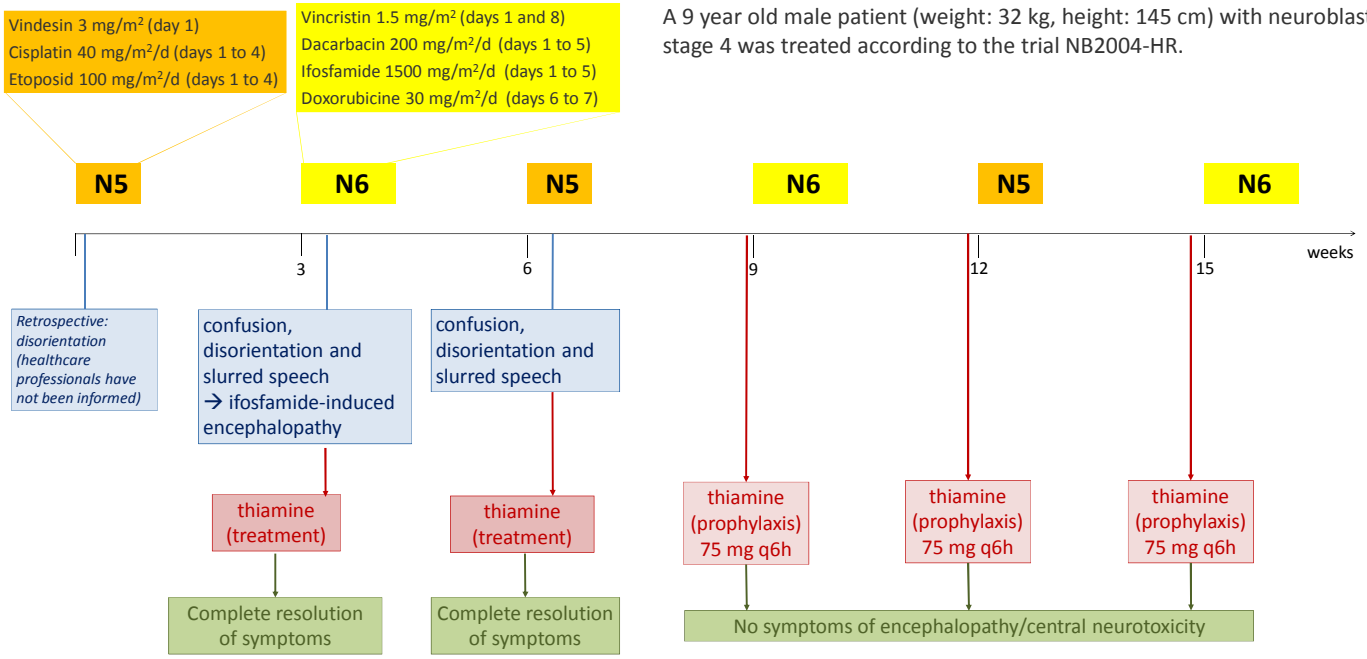


**Figure 1**: Illustration of clinical course of the patient during the relevant part of neurotoxitity of trial NB2004-HR.

## Results

Employing the widely accepted causality scales for adverse effects WHO-UMC causality categories (table 1) or Naranjo scale (table 2), it was probable that cisplatin (Naranjo score: 8, WHO-UMC: probable/likely) or etoposide (Naranjo score: 7 points, WHO-UMC: probable/likely) have caused the encephalopathy.

| Causality term | Assessment criteria |
|---|---|
| Probable/ Likely | - Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>- Unlikely to be attributed to disease or other drugs<br>- Response to withdrawal clinically reasonable<br>- Rechallenge not required |

**Table 1**: Application of the WHO UMC Causality Categories for adverse reactions causality to cisplatin and etoposide.

| | Questionnaire | Yes | No | Not known or not done | Cisplatin | Etoposide |
|---|---|---|---|---|---|---|
| 1 | Are there previous conclusive reports on this reaction? | 1 | 0 | 0 | **1** | **0** |
| 2 | Did the adverse event occur after the suspected drug was administered? | 2 | -1 | 0 | **2** | **2** |
| 3 | Did the adverse reaction improve when te drug was discontinued or a specific antagonist was administered? | 1 | 0 | 0 | **1** | **1** |
| 4 | Did the adverse reaction reappear when the drug was readministered? | 2 | -1 | 0 | **2** | **2** |
| 5 | Are there alternative causes that could have caused the reaction? | 1 | 2 | 0 | **2** | **2** |
| 6 | Did the reaction reappear when a placebo was given? | -1 | 1 | 0 | **0** | **0** |
| 7 | Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | 1 | 0 | 0 | **0** | **0** |
| 8 | Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | 1 | 0 | 0 | **0** | **0** |
| 9 | Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | 1 | 0 | 0 | **0** | **0** |
| 10 | Was the adverse event confirmed by any objective evidence | 1 | 0 | 0 | **0** | **0** |
| | **Total score** | | | | **8** | **7** |

**Table 2**: Application of the Naranjo scale for adverse reactions causality to cisplatin and etoposide (definite >/= 9, probable: 5-8, possible: 1-4, doubtful: 0 points).

## Conclusion

Several aspects support thiamine's efficacy: (1) reasonable time relationship of adverse neurologic symptoms to N5 cycle, (2) effect is unlikely to be explained by other drugs and (3) response to thiamine was reasonable. As we did not withdraw thiamine in one of the following N5 cycles, it is not possible to evaluate, whether the symptoms would have reappeared without thiamine, which would further corroborate our hypothesis.

To our knowledge, this is the first report about the successful use of thiamine against non-ifosfamide induced encephalopathy. Thiamine might provide a reasonable option for the treatment and prevention of cisplatin/etoposide-induced encephalopathy in children with neuroblastoma.



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