Antiemetic neurokinin-1 antagonist aprepitant and ifosfamide-induced encephalopathy

We report the occurrence of an acute encephalopathy following ifosfamide infusion, that we believe directly triggered by aprepitant (Emend® , Merck & Co., Inc.). Aprepitant, the first neurokinin-1 receptor antagonist, is a new antiemetic indicated for highly and moderately emetogenic chemotherapy, in association with 3-HT3 receptor antagonists and corticosteroids.

A 57-year-old woman presented with a metastatic osteosarcoma of the left calcaneum. She received her first cycle of treatment combining: ifosfamide (2.5 g/m², short i.v. on days 1–2 and 14–15), doxorubicin (30 mg/m² on days 1–2 and 14–15) and cisplatinum (50 mg/m² on days 14–15), monthly. The antiemetic regimen was the following: 125 mg aprepitant given orally 1 h before chemotherapy; 8 mg i.v. ondansetron and 60 mg i.v. methylprednisolone 30 min before chemotherapy.

Two hours after the first infusion of ifosfamide (day 1), the patient presented typical symptoms of ifosfamide-induced encephalopathy, associating marked sleepiness, dizziness, visual and auditory hallucinations. The patient fully recovered after 6 h. Methylene blue infusion was not required, given the short duration of symptoms [1]. She received the planned treatment on day 2, and the pharmacokinetics of ifosfamide and its metabolites was assessed on this occasion (Table 1). The patient experienced the same symptoms.

Since both aprepitant and ifosfamide are substrates of CYP3A4, a pharmacokinetic interaction involving this metabolic pathway was suspected.

Therefore, chemotherapy was administered on days 14–15 without aprepitant and the pharmacokinetics of ifosfamide was assessed again (Table 1). Other medications remained the same. After aprepitant withdrawal, the patient did not experience any symptoms of acute encephalopathy.

Ifosfamide is a prodrug that requires activation by hepatic cytochrome P450 (CYP), especially the 3A4 sub-type, leading to the 4-hydroxy-ifosfamide (4OH-Ifo) [2]. Ifosfamide is also converted by CYP3A4 to inactive, neurotoxic metabolites: the 2- and 3-dechloroethyl-ifosfamide (2d-Ifo and 3d-Ifo).

Following aprepitant, we observed at hour 2 an increase by 66.7% of 2d-Ifo and 37.3% of 3d-Ifo which may account for the clinical observation. The clearance of ifosfamide was also 1.6-fold higher. We noticed that the whole metabolism was stimulated.

Following aprepitant, the cytotoxic metabolite 4OH-Ifo was 28.1% higher at hour 2, and 27.7% higher at H4. The faster metabolic clearance is probably related to an inductive effect of aprepitant.

Whereas aprepitant is known to inhibit CYP3A4 [3], it can also cause a transient induction of CYP3A4 [4]. The strong

Table 1. Pharmacokinetics of ifosfamide and its metabolites

<table>
<thead>
<tr>
<th></th>
<th>Ifosfamide (µg/ml)</th>
<th>2d-Ifo (µg/ml)</th>
<th>3d-Ifo (µg/ml)</th>
<th>4OH-Ifo (µg/ml)</th>
<th>Ifosfamide half-life (min)</th>
<th>Ifosfamide clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>H0</td>
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<td>H2</td>
<td>69.2</td>
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<td>H4</td>
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<td>22.5</td>
<td>5.59</td>
<td>7.87</td>
<td>6.55</td>
<td>7.25</td>
</tr>
</tbody>
</table>

2d-Ifo, 2- dechloroethyl-ifosfamide; 3d-Ifo, 3-dechloroethyl-ifosfamide; 4OH-Ifo, 4-hydroxy-ifosfamide; APR, aprepitant; H, hour.
aprepitant-related induction of CYP3A4 observed in this case after a single administration and within few hours, questions the relevance of this observation for the daily management of cancer patients treated with ifosfamide. In order to confirm that aprepitant can favor ifosfamide-induced encephalopathy, further observations are needed.

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**references**


doi: 10.1093/annonc/mdm104