Background

Ifosfamide is an alkylating agent used to treat a variety of solid tumours. One of the side effects associated with the use of ifosfamide is ifosfamide-induced encephalopathy. Methylene blue has been used as both a treatment for and prophylaxis of ifosfamide induced encephalopathy.

Indications for use

The use of methylene blue treatment dose may be considered for patients experiencing grades III and IV central neurotoxicity\(^1\) based on National Cancer Institute common toxicity criteria. Prophylaxis should be considered for patients who have experienced grades III and IV neurotoxicity in previous cycles.

Table 1: NCI common toxicity criteria: neurocortical toxicity

<table>
<thead>
<tr>
<th>GRADE</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms:</td>
<td>None</td>
<td>Mild somnolence or agitation</td>
<td>Moderate somnolence or agitation</td>
<td>Severe somnolence, agitation, confusion, disorientation, or hallucinations</td>
<td>coma, seizures, toxic psychosis</td>
</tr>
</tbody>
</table>

Dose

Whilst there have been no studies to determine the best dose and scheduling for the treatment of ifosfamide-induced encephalopathy with Methylene Blue, a review of the literature\(^1,2,3,4\) would suggest:

Treatment of Ifosfamide-induced encephalopathy (all ages):
1mg/kg IV (max 50mg) every four hours

Prophylaxis of Ifosfamide-induced encephalopathy (all ages):
1mg/kg IV (max 50mg) every six hours
**Administration**

The preparation is a 0.5% solution of methylene blue i.e. 5mg in 1ml. It can be administered undiluted as a slow IV bolus (over 5 minutes). It can also be diluted in 50mL glucose 5% if the volume to be administered is too small. Dilution is preferable due to the solution being hypotonic and causing local injection pain. Due to extreme pH of the product, give via central line if possible.

*Not to be injected intrathecally or subcutaneously.*

**Side effects**

The most commonly reported adverse reactions are nausea, abdominal and chest pain, headache, dizziness, tremors, anxiety, confusional state, dyspnoea, tachycardia, hypertension, the formation of methaemoglobinemia, dysgeusia, injection site pain and pain in extremities.

See SPC for less common side effects.

Intravenous injection of methylthioninium chloride has occasionally caused hypotension and cardiac arrhythmias, and such disorders might prove fatal on rare occasions.

Other effects:
- Hypersensitivity reaction including anaphylaxis
- Staining of tissues, urine and faeces blue/green
- Extravasation can cause tissue necrosis

**Cautions**

- Extreme caution should be exercised when administering to newborns and infants below the age of 3 months due to lower concentrations of NADPH-methaemoglobin reductase. This is necessary for reducing methaemoglobin to haemoglobin, making these infants more susceptible to methaemoglobinemia produced by high doses of methylthioninium chloride.
- Use with care in renal insufficiency.
- Caution if patient is taking SSRIs (selective serotonin reuptake inhibitors), bupropion, buspirone, clomipramine, mirtazapine, and venlafaxine.
- Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide co-administration.
- Can exacerbate dapsone induced haemolytic anaemia

**Contraindications**

- Hypersensitivity to the active substance, or to any other thiazine dyes
- Patients with Glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of haemolytic anaemia
- Patients with nitrite-induced methaemoglobinemia during treatment of cyanide poisoning
- Patients with methaemoglobinemia due to chlorate poisoning
- Deficiency in NADPH (nicotinamide adenine dinucleotide phosphate) reductase
Monitoring during treatment

Standard monitoring of neurological status
ECG and blood pressure monitoring

REFERENCES


RELATED DOCUMENTS AND PAGES

None

AUTHORISING BODY

Paediatric Haematology, Oncology and Bone Marrow Transplant Quality Assurance Forum (QuAF)

SAFETY

Methylene Blue solution **must not** be injected intrathecally or subcutaneously

QUERIES AND CONTACT

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