Methylthioninium Chloride (Proveblue®) for the Treatment and Prophylaxis of Ifosfamide Induced Encephalitis

Introduction

Ifosfamide is an alkylating agent used to treat a range of solid and haematological malignancies. Its use can lead to central nervous system (CNS) toxicity in 10-30% (mean 12%) of patients after intravenous administration. The onset of symptoms occurs between 12 and 146 hours after the start of administration. CNS toxicity is increased by 50% with oral administration due to differences in metabolism between the two routes. Methylthioninium chloride (Proveblue®) is not licensed for the treatment of ifosfamide induced encephalopathy (IIE), so its use is off-label. Its mechanism of action is unclear, it is proposed that its activity as an electron acceptor reduces the formation of the toxic metabolite chloroacetaldehyde.

Risk Factors

- Low albumin
- Poor renal function
- Tumour in the lower abdomen and pelvis
- Pre-treatment with cisplatin
- Prior CNS disease

Presentation

- Confusion is the most common symptom of IIE, ranging from transient lethargy or increased drowsiness to frank delirium
- Hallucination or psychosis occurs in up to 30% of patients
- Incontinence and muscle twitching are present in about 9% of patients
- Less common manifestations (<5% of patients) include extrapyramidal symptoms, cranial nerve abnormalities, seizures, mutism, dysarthria, amnesia, blurred vision, hearing loss and asterixis

Treatment

- Mild somnolence or agitation
  - Monitor neurological status (standard neurological observations)
  - Ensure ifosfamide infusion is running no faster than 1g/m²/hour
- Moderate somnolence or agitation
  - As above and:
    - Start methylthioninium chloride (Proveblue®) 50mg IV 4 hourly
    - Continue methylthioninium chloride (Proveblue®) until all signs of neurotoxicity have resolved
    - Consider prophylactic methylthioninium chloride (Proveblue®) with next cycle
    - If neurotoxicity worsens, stop ifosfamide
- Presence of any of the following: severe somnolence, agitation, confusion, disorientation, hallucinations, coma, seizures or toxic psychosis
  - Stop ifosfamide (continue mesna as per protocol)
  - Start methylthioninium chloride (Proveblue®) 50mg IV 4 hourly
Consider ITU review and other supportive measures
- Monitor neurological status (standard neurological observations)
- Continue methylthioninium chloride (Proveblue®) until all signs of neurotoxicity have resolved
- Further treatment with ifosfamide should be avoided.

**Prophylaxis of Ifosfamide Induced Encephalopathy**

Consider in patients with:
- Previous IIE
- Serum creatinine >150 μmol/L
- Serum albumin <30

The following nomogram can be used to aid decision making, regarding the use of prophylactic methylene blue. Pre-treatment albumin and creatinine should be measured and a ruler placed across the two values, use the relevant scale depending on the presence of pelvic disease.

![Nomogram](image)

**NOTE: Values are the probability of remaining free of CNS toxicity**

If a patient is at high risk of encephalopathy, glucose-6-phosphate dehydrogenase deficiency (G6PD) status should be checked before treatment is started, as this contraindicates the use of methylthioninium chloride (Proveblue®).

Prophylactic dose of methylthioninium chloride (Proveblue®): 50mg IV 6 hourly
Administration Instructions

- Dilute methylthioninium chloride (Proveblue®) 50mg in 50ml glucose 5%
- Give over a minimum of 5 minutes
- If available, deliver through a central venous device (due to low pH of 3-4.5)
- Flush with glucose 5% (30ml at same rate, then 70ml at a rate of 1000ml/hour)

Contraindications to Methylthioninium Chloride (Proveblue®)

- Patients with G6PD due to the risk of haemolytic anaemia
- Patients with nitrite-induced methaemoglobinaemia during treatment of cyanide poisoning
- Patients with methaemoglobinaemia due to chlorate poisoning
- Deficiency in NADPH (nicotinamide adenine dinucleotide phosphate) reductase

Adverse Events

Most common: dizziness, paraesthesia, dysgeusia, nausea, skin discoloration, chromaturia, sweating, injection site pain and pain in extremity

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

Supply Out of Hours

Emergency department (CGH and GRH sites) and Rendcomb side rooms (CGH) keep as stock.

References

- London Cancer North and East. Guidelines for the Use of Methylene Blue for the Treatment and Prophylaxis of Ifosfamide-Induced Encephalitis. Jan 2014