

# Methylthioninium Chloride (Proveblue<sup>®</sup>) 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<sup>®</sup>) 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/m<sup>2</sup>/hour
- Moderate somnolence or agitation
  - As above and:
  - Start methylthioninium chloride (Proveblue<sup>®</sup>) 50mg IV 4 hourly
  - Continue methylthioninium chloride (Proveblue<sup>®</sup>) until all signs of neurotoxicity have resolved
  - Consider prophylactic methylthioninium chloride (Proveblue<sup>®</sup>) 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<sup>®</sup>) 50mg IV 4 hourly

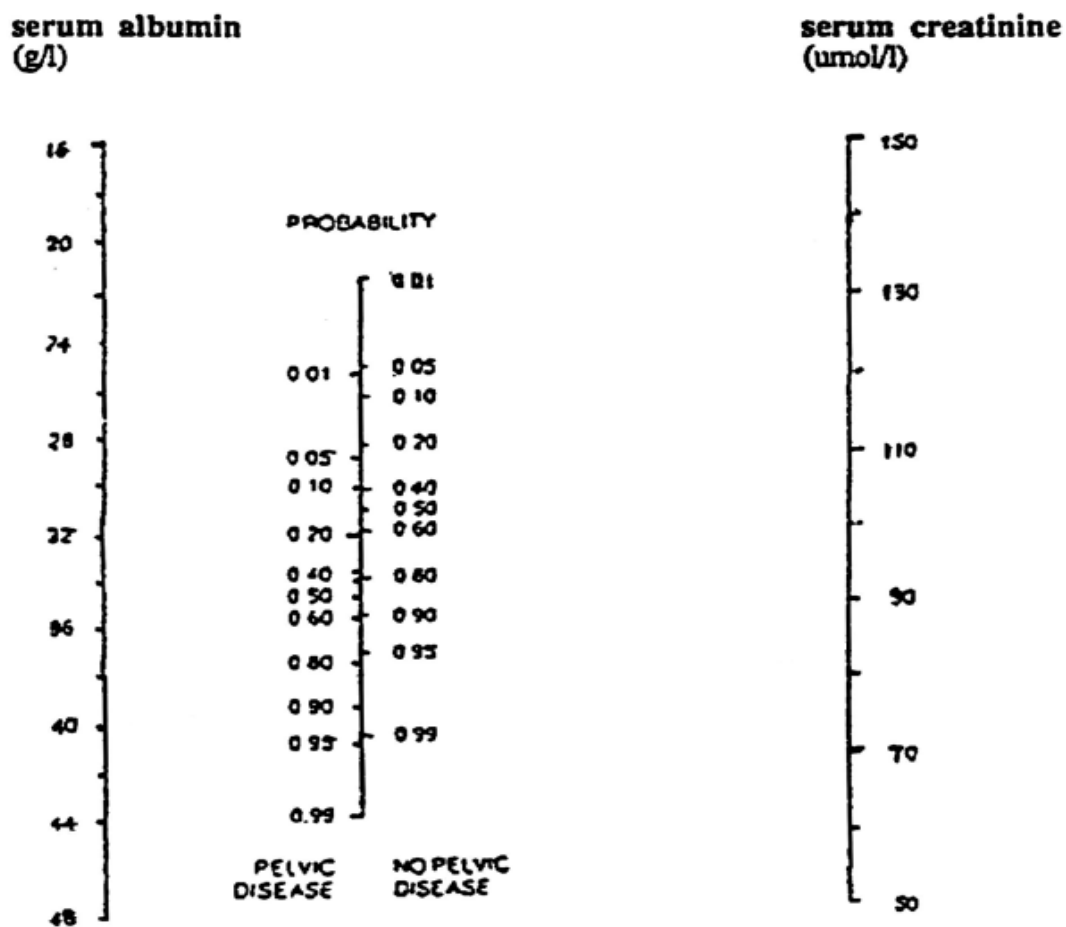
- Consider ITU review and other supportive measures
- Monitor neurological status (standard neurological observations)
- Continue methylthioninium chloride (Proveblue®) until all signs of neurotoxicity have resolved
- Further treatment with ifosfamide should be avoided.

### 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.



**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

- Ajithkumar, T., Parkinson, C., Shamshad, F. and Murray, P. (2006). *Ifosfamide Encephalopathy*. Clin Oncol (R Coll Radiol). 19(2):108-14.
- Injectable Medicines Guide. Methylthioninium chloride (methylene blue) monograph. <http://medusa.wales.nhs.uk/IVGuideDisplay.asp>. [Accessed on 1/12/17]
- London Cancer North and East. Guidelines for the Use of Methylene Blue for the Treatment and Prophylaxis of Ifosfamide-Induced Encephalitis. Jan 2014
- Martindale (2017). *Methylthioninium chloride Proveblue 5 mg/ml solution for injection*. [online] electronic medicines compendium. Available at: <http://www.medicines.org.uk/emc/medicine/30489> [Accessed 1 Dec. 2017].
- Meanwell, C., Blake, A., Kelly, K., Honigsberger, L. and Blackledge, G. (1986). *Prediction of Ifosfamide/Mesna associated encephalopathy*. Eur J Cancer Clin Oncol 22 (7), pp. 815-819.
- Patel, P. (2006). Methylene Blue for Management of Ifosfamide-Induced Encephalopathy. *Annals of Pharmacotherapy*, 40(2), pp.299-303.