Pharm-11B7 Briefly outline the acute management of malignant hyperthermia (during a relaxant general anaesthetic). Describe the important aspects of dantrolene pharmacology relevant to treating malignant hyperthermia.

**Background**

*Malignant hyperthermia* (MH) = acute life-threatening disturbance of skeletal muscle calcium homeostasis following exposure to triggering agent (e.g. volatiles, suxamethonium, etc) resulting in:
- hypermetabolic state → \(\uparrow\) \(O_2\) consumption, \(\uparrow\) \(CO_2\) production
- muscle rigidity (*masseter spasm, trismus, etc*)
- hyperthermia
- acidosis and hyperkalaemia (*cardiac arrhythmias*)

Prevalence – approx 1:15,000 (*range 1:10,000 ~ 220,000*)

**MH Management**

**Immediate actions:**
- stop triggering agent (volatiles, suxamethonium)
- remove vaporiser
- hyperventilate with 100% \(FiO_2\) at \(\geq 10\)L/min fresh gas flow
- delegate personnel to prepare *dantrolene* (iv 2.5 mg/kg rapid bolus)
- either wake patient up or convert to propofol TIVA

**Adjuvant actions:**
- active cooling (ice bath, lavage, cold IV saline) if \(T \geq 38.5\) °C
- treat hyperkalaemia
- consider treating acidosis with \(NaHCO_3\)
- do NOT give calcium channel blockers (interaction with dantrolene to produce significant hyperkalaemia)
- additional monitoring (arterial line, central line, urinary catheter)
- induce diuresis

**Post-resuscitation management**
- HDU/ICU admission
- Medialert bracelet
- testing of family members (autosomal dominant inheritance pattern)

**Dantrolene Pharmacology**

**Physicochemical**
Formulation – orange powder, vials of 20 mg
Need to dissolve in \(H_2O\) for intravenous injection (*poor solubility, difficult to dissolve*)
Venous irritant → may cause thrombophlebitis ± tissue necrosis if extravasated

**Pharmacokinetics**

**Absorption** – IV and PO
**Distribution** – $V_D$ 0.6 L/kg; 90% protein bound

**Metabolism** – hepatic metabolism; major metabolite is 5-hydroxydantrolene, which is active

**Elimination** – renally excreted, half-life 9 hours (*Stoelting 5th*)

**Pharmacodynamics**

**Dose** – 2.5 mg/kg bolus, repeat

**Mechanism** – competitive antagonist at sarcoplasmic reticulum Ryanodine receptors
\[ \downarrow \text{Ca}^{2+} \text{ release by SR} \rightarrow \downarrow \text{excitation-contraction coupling} \rightarrow \downarrow \text{skeletal muscle metabolism} \]

**CNS** – sedation, speech and visual disturbances

**CVS** – minimal effects

**RESP** – minimal effects

**GIT** – ↓ appetite, nausea/vomit, abdominal pain, diarrhoea, hepatic dysfunction (may be fatal)

**MSK** – weakness, potentiate non-depolarising NMBs

**Examiner’s comments**

Equal weighting was given to each part of the question. Most of the candidates who did not attempt the second part of the question did not achieve a pass mark.

A brief definition of malignant hyperthermia (MH) was expected. Lengthy discussion of the different ryanodine receptors was not required. The acute management of malignant hyperthermia was generally well described. An outline of specific tasks and actions was required, such as “hyperventilate with 100% oxygen at flows of greater than 10 litres per minute”. Statements like “provide airway support” or “obtain an ICU consult” are too nonspecific. It was pleasing to see descriptions of the anaesthetist in recruiting help, and as leader and coordinator of the team response in theatre. Most candidates understood the pharmaceutical aspects of dantrolene. With respect to pharmacokinetics, candidates often resorted to guesswork. Dantrolene is metabolised in the liver.

- The major pathway produces 5 hydroxy-dantrolene (which is active).
- A minor pathway produces an inactive metabolite.

Both metabolites are cleared renally. The half life of dantrolene is variably reported between 5-10 hours. Further dantrolene doses may be required in intensive care. Dantrolene binds to the ryanodine receptor in skeletal muscle, inhibiting calcium release from the sarcoplasmic reticulum. Side effects of dantrolene are rare. The alkaline solution can cause thrombophlebitis, and skin necrosis can occur if the solution extravasates. Hepatic dysfunction (including fatal hepatic failure), sedation
and gastrointestinal side effects have been described. Mild to moderate skeletal muscle relaxation occurs. Dantrolene has no direct cardiac effects. The diluent volume required to administer large doses of dantrolene may precipitate acute pulmonary oedema. Co-administration of verapamil is associated with marked hyperkalaemia, which may precipitate ventricular fibrillation. Dantrolene potentiates the skeletal muscle relaxation of non-depolarising muscle relaxants.