TO REPORT AN ADVERSE DRUG REACTION

Online
2. Click on ‘Report an Adverse Event’.
3. Click to report as a healthcare professional and choose ‘Online Reporting’.
4. Submit the form once completed.

Mail
1. Print out and complete the ADR form available from our website.
2. Mail or fax to:
The Pharmacovigilance Section,
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health, Malaysia.
Lot 36, Jalan Universiti,
46200 Petaling Jaya, Selangor.

Telephone
03-7883 5400
(ext. 8460/ 8461/ 8463)

Fax
03-7956 7151

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Ketamine: Risk of Severe Liver Damage with Repeated and/or Prolonged Use at High Doses

Overview
Ketamine is an NMDA-receptor antagonist used for general anaesthesia and sedation. It has anaesthetic and analgesic properties, depending on the dose administered. Ketamine is used in subanaesthetic doses for control of acute and chronic pain, especially severe forms with evidence of central sensitisation not well-controlled with other agents. It is usually combined with an opioid for acute pain.

Background of the Safety Issue
The French National Agency for the Safety of Medicines and Health Products (ANSM) published a Dear Healthcare Professional Communication (DHPC) letter on the risk of severe liver damage during repeated and/or prolonged use of high-dose ketamine.

Ten (10) cases of serious liver damage (cholestatic cholangitis), including four (4) which led to liver transplantation, have been reported to the ANSM since 2014. These may be linked to repeated or prolonged use of ketamine (between 1-5 months of continuous use) at high doses in the management of severe pain (exceeding 100mg/day continuous over several days) or severe burns (200-400mg/hour in 3-6 hours).

Healthcare professionals in France were reminded to follow the recommended dosage for palliative care practice at 0.5mg/kg/day (continuous IV infusion) with increments of 0.25mg/kg/day. Treatment should be initiated by a team specialised in the management of pain or palliative care with close observation and monitoring, including liver function monitoring.

Local Scenario
Currently there are two (2) products containing ketamine that have been registered in Malaysia, with approved indications including:
- Sole anaesthetic for diagnostic and surgical procedures that do not require skeletal muscle relaxation.
- Induction of anaesthesia prior to the administration of other general anaesthetic agents.
- As a supplement to low potency agents, such as nitrous oxide.
- May be used in children as intense analgesic for management of minor surgical and diagnostic procedures or repeated procedures, e.g. changing burn dressing.

Adverse Drug Reaction (ADR) Reports
The NPRA has received a total of 24 reports with 34 adverse events related to ketamine. The most reported adverse event was tonic-clonic convulsions (5, 14.7%), followed by maculopapular rash (3, 8.8%) and urticaria (3, 8.8%). To date, no case of liver damage associated with ketamine has been reported to the NPRA.

Advice for Healthcare Professionals
- Please comply with the recommended dosing for ketamine especially with repeated and/or prolonged use.
- Monitor patient’s liver function closely if repeated and/or prolonged high dose of ketamine is used.
- Please report all adverse events suspected to be related to the use of ketamine to the NPRA.

Recombinant Human Erythropoietins: Risk of Severe Cutaneous Adverse Reactions (SCARs)

Overview
The hormone erythropoietin is essential for the formation of red blood cells. Recombinant human erythropoietins are indicated for the treatment of anaemia in patients with certain conditions, such as chronic renal failure or non-myeloid cancer patients who develop anaemia after chemotherapy.

In the European Union (EU), post-marketing reports of severe cutaneous adverse reactions (SCARs), in particular Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), led to this safety signal being identified and analysed by the European Medicine Agency’s Pharmacovigilance Risk Assessment Committee (PRAC).

All cases (including data from the EudraVigilance database and marketing authorisation holders) were analysed for all recombinant human erythropoietins. The most commonly reported adverse event was tonic-clonic convulsions (5, 14.7%), followed by maculopapular rash (3, 8.8%). To date, no case of liver damage associated with recombinant human erythropoietins has been reported to the NPRA.

Local Scenario
There are currently 15 products containing recombinant human erythropoietins (darbepoetin alfa, epoetin alfa, epoetin beta, epoetin zeta and methoxy polyethylene glycol-epoetin beta) registered with the Drug Control Authority. Following review of this safety issue, product registration holders will be required to update the package inserts of recombinant human erythropoietins in Malaysia with safety information related to the risk of SCARs.

Adverse Drug Reaction (ADR) Reports
Between year 2000 to May 2017, the NPRA has received 213 ADR reports with 289 adverse events suspected to be related to recombinant human erythropoietins. The most commonly reported adverse events include rash, itching and pure red cell aplasia. To date, the NPRA has received one (1) report of SCARs related to recombinant human erythropoietins, where a 37-year-old female patient developed TEN (confirmed by skin biopsy) after the first dose of subcutaneous epoetin beta 2000 IU. The patient was treated with intravenous immunoglobulin for four days and her condition had improved at the time of ADR reporting.

Advice for Healthcare Professionals
- Severe cutaneous adverse reactions, some life-threatening or fatal, including cases of SJS and TEN have been reported in patients treated with recombinant human erythropoietins.
- Patients should be monitored and advised on the signs and symptoms of severe skin reactions when starting treatment with a recombinant human erythropoietin product.
- Patients should be instructed to stop recombinant human erythropoietin treatment and contact their doctor immediately if they develop:
  - flu-like symptoms including fever, tiredness, muscle and joint pain, followed by a widespread rash with reddening and blistersing of the skin and oral mucosa, eyes, nose, throat, or genital area.

References: