GRANISETRON

Introduction

Granisetron is a potent and highly **selective 5-HT_3 serotonin receptor antagonist.**

It is an effective antiemetic agent that does not act via dopamine blockade of the older antiemetic agents.

It is especially useful in cases of nausea and vomiting caused by radiotherapy or chemotherapeutic agents as well as the control of post-operative nausea and vomiting.

Unlike older anti-dopaminergic antiemetic agents, Granisetron is suitable for use in children.

Granisetron is most commonly given intravenously.

History

Granisetron was developed by chemists working at the British drug company Beecham in the late 1980s.

Preparation

Preparations include:

Ampoules: **1 mg in 1 mL , 3 mg in 3 mL**

Tablets: **2 mg**

Mechanism of Action

Granisetron, (and its analogues, dolasetron, ondansetron, tropisetron and palonosetron), selectively antagonize **serotonin 5-HT_3** receptors in the central nervous system and peripherally

These receptors are particularly important in emesis stimulated by cytotoxic drugs.

These receptors are also in the gastrointestinal tract and may be involved in local initiation of the vomiting reflex

Its precise mode of action in the control of nausea and vomiting is unknown but chemotherapeutic agents and radiotherapy may cause release of 5HT in the small

intestine, initiating a vomiting reflex by activating vagal afferents via $5HT_3$-receptors. Ondansetron blocks the initiation of this reflex.

Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is due to antagonism of $5HT_3$-receptors on both peripheral and central neurones.

The mechanisms of action in postoperative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting

Granisetron does not have any appreciable effect on other receptors such as dopamine D_2, muscarinic, $alpha_1$, $alpha_2$, beta adrenoreceptors, histamine H1 receptors, benzodiazepine, receptors or opioid receptors.

Pharmacokinetics

Absorption:

- Granisetron is given **intravenously** or **orally**
- Granisetron is rapidly and completely absorbed after oral administration with peak plasma concentrations being reached at approximately two hours.
- Bioavailability is about 60 %.
- It should *not* be given IM

Distribution:

- Granisetron is extensively distributed with a mean volume of distribution of approximately 3 L/kg.
- Plasma protein binding is approximately 65%.

Metabolism and excretion:

- Granisetron is rapidly metabolized in the liver.
- The mean plasma half-life of granisetron in patients is around nine hours but there is wide inter-subject variability.

Indications

1. Nausea and vomiting in general.

In particular, nausea and vomiting in the settings of:

2. Radiotherapy

3. Chemotherapy:

    - Granisetron is more effective for *acute* (i.e. within 48 hours) than delayed symptoms of cancer chemotherapy - induced nausea and vomiting. [2]

4. Post-operation:

    - Ondansetron is effective in preventing postoperative nausea and vomiting when given at the end of surgery. It less effective in treating *established* postoperative nausea and vomiting.

Contraindications/ Precautions

Precautions include:

- Hypersensitivity to granisetron

Pregnancy

Granisetron is classed as B1 category drug with respect to pregnancy. [1]

Class B1 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Breastfeeding

Caution, insufficient data

Adverse Effects

- Possible allergic reactions.

Otherwise most other adverse effects are uncommon, and usually mild and transient only.

They may include:

- Headache.
- Sedation
- Anxiety/ agitation

- Constipation.
- Transient flushing and visual disturbances may occur with **rapid intravenous** injection.

Dosing

In general terms:

Adults:

- **Granisetron 1 mg IV.** [1]
- The maximum adult dose of granisetron is 9 mg / 24 hours. [3]

Children:

- **Granisetron 0.04 mg/kg (up to 1 mg) IV** [1]

Higher doses may be used, under the supervision of an oncologist, in the setting of radiotherapy and chemotherapy

References

1. eTG - March 2014
2. Granisetron in Australian Medicines Handbook
3. **Granisetron** in MIMs
4. Paul Young, Critical Care Drug Manual, Wellington Hospital Intensive Care Unit, 2010.

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