Transdermal Granisetron in the Treatment of Hyperemesis Gravidarum

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Background

Nausea and vomiting is common in early pregnancy.[1] Hyperemesis Gravidarum (HG) is a severe form of nausea and vomiting characterised by hypovolaemia and weight loss.[1,2] HG occurs less frequently, affecting around 0.3-1% of pregnancies.[2] It is the most common cause of hospitalisation in early pregnancy.[2]

Maternal complications include malnutrition and multiple vitamin deficiencies.[2] Oesophageal trauma may result from prolonged vomiting.[2] Although a casual relationship is uncertain, HG is associated with psychological morbidity, including social dysfunction, anxiety, insomnia, and depression.[2] The physical and psychological burden of HG has also been associated with elective termination of pregnancy.[2] Foetal complications include preterm birth, low birthweight and small-for-gestational age.[2]

Treatment of HG involves multiple pharmaceutical agents, including antiemetics and other medications, contributing to significant tablet and financial burden (see figure 1). Ondansetron is used where first-line antiemetics have failed, and preferably after the first trimester of pregnancy, due to mixed safety data.[3] A large retrospective study found no increased risk of major birth defect, stillbirth, preterm labour or small-for-gestational age. Other studies have found a possible association with cardiovascular defects and cleft palate with first trimester exposure.[3]

Objectives

This report aims to share our experience of using oral and transdermal granisetron to improve HG, thereby contributing to current limited evidence.

Literature Review

Granisetron is a selective 5-hydroxytryptamine (5-HT_3) receptor antagonist indicated for chemotherapy-induced or post-operative nausea and vomiting.[4] Currently there is limited safety and efficacy data for granisetron use in pregnancy and it is categorised B1 per the Therapeutic Goods Administration (TGA).[4] Studies by Aleyasin of 32 women, and Caritis of 16 women, concluded that oral and transdermal granisetron decreased nausea and vomiting in pregnancy.[5,6] A further study by Shapira of 80 women found no association with adverse neonatal outcomes.[7]

Clinical Features

A 28-year-old primip, with unremarkable previous medical history, presented to the Obstetric Medicine Outpatient Clinic at the Royal Brisbane and Women's Hospital at 24 weeks gestation for HG management on the background of multiple hospital admissions. Her symptoms included unrelenting nausea with associated vomiting. This occurred throughout the day, and of particular concern, for 2 hours each morning. Interestingly, her symptoms were unrelieved by oral ondansetron and prochlorperazine. The patient experienced reduced oral intake, weight loss, inability to work and reduced quality of life.

Figure 1: visual representation of our patient's medications required or related to the management of HG

Drug	Ondansetron	Granisetron	
Form	Oral	Oral	Transdermal
Half life	3-6.2 hours	9 hours	3-14 hours
Peak	1.6-2.2 hours	1.9 hours	48 hours
Duration of action	8 hours	24 hours	24-168 hours

Table 1: pharmacokinetic profile of ondansetron and granisetron[8,9]

Patient Progress and Outcomes

Vomiting/ Nausea

- Vomiting unrelieved by antiemetics, resulting in multiple hospital admissions and need for intravenous fluids.
- Patient unable to take ondansetron in the morning due to vomiting on waking. Trial of bedtime dosing was ineffective.

Oral granisetron

- Decision made to trial *oral* granisetron at night in place of ondansetron, due to longer half life and duration of action, with the aim to improve morning emesis (see table 1). Patient 27 weeks gestation at granisetron initiation.
- Patient counselled extensively regarding minimal studies on safety data of granisetron with no harm identified.[5-7]

Transdermal granisetron

- Patient reported improvement for 2-3 days post intervention with oral granisetron and subsequent return of vomiting thereafter.
- Decision to trial *transdermal* granisetron in place of oral at 28 weeks gestation. Treatment failure postulated due to poor absorption in the setting of HG.
- Patch applied at time of last oral dose. Decision made according to plasma concentration of transdermal granisetron at 24 hours (see figure 2).

Symptom improvement

- On patch initiation patient reported weight gain of 2kg in 1 week, secondary to improved oral intake.
- Patient reported subsequent patch peeling due to poor adhesion to skin, particularly at day 3 post application. This correlated with return of vomiting and hospital admission.

Medication review

- A review of literature around granisetron transdermal patch adhesion found that in a clinical trial of 621 patients, patch detachment occurred in less than 1%.[9] Despite this, multiple patient reports of early detachment were found.
- Technique of application assessed. Plan made to replace patch twice weekly, as patch begins to fall off.

Successful delivery

- Further improvement following twice-weekly application. Some nausea at day 3, correlating with loss of adhesion, which was managed with oral prochlorperazine.
- Transdermal granisetron continued resulting in a reduction of hospital admissions and successful vaginal delivery of healthy baby girl at 36+5 (weight:2498g, APGAR:8,9)

Pharmacist Interventions

- Advice on switch from oral to transdermal forms, including timing of last oral dose.
- Assessment, literature review and advice around patch adhesion and application
- Recommendation to increase frequency of patch application, taking into consideration pharmacokinetics and peak plasma concentration (see figure 2).
- Educating the patient on medications including potential adverse effects and safety in pregnancy.
- Sourcing stock, given special access scheme requirements of transdermal product.

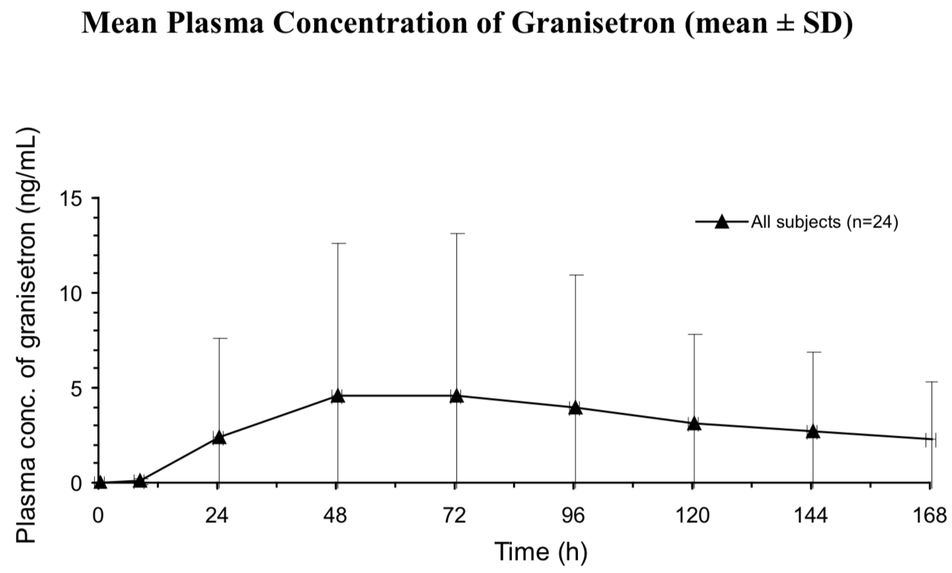

Figure 2: Mean plasma concentration curve of transdermal granisetron[10]

Conclusion

Granisetron, particularly in transdermal form, drastically improved symptoms of HG, evident by a reduction of nausea, cessation of vomiting, improved oral intake and weight gain. Granisetron use also led to a reduction in hospital admissions and associated healthcare costs. Granisetron in the future, may form part of the standard therapy for HG although this requires further research. This case highlights that alternative routes may be necessary in the treatment of HG. In our patient a successful vaginal delivery of a healthy baby girl weighing 2498g at 36 weeks and 5 days was achieved.

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