Hyperemesis Gravidarum: the clinical relevance and current use of anti-emetic medications

Sarah Beatty
Fourth Year Medical Student
School of Medicine
University of Auckland

Sarah is a fourth year medical student at Auckland University with a prior BSc and outside interests in practically everything including: music, art, humanitarian issues, philosophy and cultures/languages. I've also been involved with medical research, with hyperekplexia being the main research interest. The hyperemesis gravidarum article was written for a General Practice learning needs paper.

ABSTRACT

Hyperemesis Gravidarum is best defined as intractable nausea and vomiting during pregnancy, and is characterised by dehydration, ketonuria, electrolyte disturbance and weight loss[1,2]. Affected women experience significantly reduced quality of life and there remains no evidence of adequate pharmacological treatment. The pathophysiology of HG is also indistinct with human chorionic gonadotropin and estrogen believed to contribute. Management of nausea and vomiting during pregnancy typically falls within the domain of the General Practitioner. Anti-emetics which may be considered in this scenario include dopamine and histamine antagonists, serotonin receptor antagonists and

corticosteroids. Here, a pyridoxine-metoclopramide combination is suggested to be the first-line therapy for HG.

INTRODUCTION

For centuries, physicians have searched for a treatment to counteract Hyperemesis Gravidarum, best defined as intractable nausea and vomiting during pregnancy and characterised by dehydration, ketonuria, electrolyte disturbance and weight loss. At best, hyperemesis gravidarum not only severely reduces quality of life for women during pregnancy, but also contributes an extreme financial burden and loss of paid hours of work to society. At its most severe, the condition is a leading cause for hospitalization during pregnancy. It poses a significant threat to both mother and fetus and was once considered an important cause of maternal mortality. Despite medical evidence that 70-85% of women experience nausea and vomiting during pregnancy and up to 3% of these women experience hyperemesis gravidarum, there remains no proven evidence of adequate pharmacological treatment.

Early treatments for hyperemesis gravidarum which proved unsuccessful include anti-psychotics, vitamins and tranquilisers. More recent therapies have included pyridoxine (vitamin B6) and doxylamine combinations, H1 receptor antagonists, dopamine receptor blockers and serotonin antagonists. Based on evidence that they may reduce emesis resulting from cancer chemotherapy, corticosteroids have also recently been trialled as a treatment for hyperemesis gravidarum (HG). However, Bsat et al. commented that corticosteroids and serotonin receptor antagonists such as ondansetron, are more commonly used following failure of first-line therapy. Importance however, must be placed in assessing the relevance of the available anti-emetic medications in relation to the physiological cause of HG.

PHYSIOLOGY OF HG

Despite much speculation, the pathophysiology of HG remains largely elusive. There is general agreement amongst the scientific community that the condition arises from a placental source, most often considered to be human chorionic gonadotropin (hCG). However, estrogen has also been noted to be a recognised potential hormonal contributor.

Because all pregnant women exhibit increases in serum hCG and estrogen, the physiological response to these hormones in women who develop HG is believed to be dictated by genotypic and psychological factors, in addition to response of the gastrointestinal, vestibular and olfactory systems. Sullivan et al. postulate that the vomiting reflex arc forms a component of HG, suggesting therefore the importance of the serotonin receptors which are central to this reflex. The use of histamine receptor antagonists and dopamine receptor blockers suggests that these receptors may also mediate HG. Yost et al. propose that the chemoreceptor trigger zone in the brainstem which is responsible for nausea and vomiting may be modified by corticosteroid administration, a possibility echoed by Safari et al., who remark however, that the involvement of this centre in HG is unclear. The fact that the physiological processes involved in HG have never been adequately proven is postulated to be a large contributor to the perplexity surrounding management of the condition within the field of General Practice.

EVIDENCE FOR USE OF ANTI-EMETICS

Dopamine and Histamine Receptor Antagonists

A recent study conducted by Bsat et al., considered the use of three commonly administered medications for nausea and emesis associated with pregnancy. Pyridoxine-metoclopramide (a dopamine receptor antagonist), prochlorperazine (a dopamine and histamine receptor antagonist) and promethazine (a histamine receptor antagonist) were administered to three groups of study participants in the first trimester of a singleton pregnancy over a three day period. Despite the fact that

the pyridoxine-metoclopramide required an intramuscular injection, this was not perceived as being problematic to the patient. This combination was also reportedly the most effective, reducing emetic episodes from an average of 2.3 to 0.6 over the three days of treatment. Promethazine demonstrated a similar efficacy, reducing emetic episodes from 2.4 to 0.8, whereas prochlorperazine reduced such episodes from 2.3 to 1.1. Additional to central antagonism of the dopamine receptor, Bsat et al. also described the gastro-intestinal effects of metoclopramide which may be relevant in reducing HG. Although promethazine also demonstrated efficacy in reducing symptoms of nausea and vomiting, the sedating effect of promethazine is significantly more persistent than compared to metoclopramide. This finding, in conjunction with the symptomatic results of the three therapies indicates that the pyridoxine-metoclopramide combination has a place as one of the first line treatments for HG.

Serotonin Receptor Antagonists

The serotonin receptor antagonist featured most prominently in literature for treating nausea and emesis is ondansetron. Sullivan et al. conducted a study extending over 17 months comparing this treatment with promethazine, postulating that the anti-emetic effects of this medication may extend to the intractable hyperemesis experienced in HG. As noted by Bsat et al., promethazine was mentioned as a popular first-line anti-emetic medication, and was for this reason selected by Sullivan et al. as comparison for efficacy of ondansetron. Response to treatment between the two groups was investigated using both subjective assessment by study participants and objective assessment using measurable clinical parameters. At all levels of investigation, ondansetron proved no more effective than promethazine in treatment patients with HG. Interestingly however, sedation was elicited in more than 50% of the study population assigned to promethazine compared with only 13% of the study population assigned to ondansetron. Similar to results demonstrated by Bsat et al., this finding suggests that non-sedating treatments with similar efficacy profiles to the current first-line treatment, promethazine are available and should be considered for use in HG.

Corticosteroids

Despite over-riding similarities in study design, recent studies by Yost et al. and Safari et al. offer diverse conclusions regarding the use of corticosteroids (predominantly methyl-prednisolone) in HG[3,5]. Whilst Safari et al. report improvements in symptom profile and reduction in hospitalization following treatment of participants[5], Yost et al. demonstrate no reduction in hospitalizations between treatment and control groups[3]. Interestingly, promethazine was the control treatment used for research by Safari et al., whilst all participants in the study by Yost et al. received promethazine and metoclopramide[3,5]. Whilst Safari et al. provided evidence of shortened duration of HG with methyl-prednisolone therapy; Yost et al. stated that their findings supported those of a recent evidence-based review, with methyl-prednisolone not reducing number of hospital admissions for symptomatic HG[3,5].

CONCLUSION

Recent evidence examined indicates the frequent use of promethazine as a first-line therapy in the treatment of HG[2-5]. Studies have provided evidence that this medication remains superior to other trialled treatments including methyl-prednisolone and ondansetron (a serotonin receptor antagonist)[2-5]. However, evidence also identifies the potential for replacement of promethazine as a first-line anti-emetic treatment with a pyridoxine-metoclopramide combination which not only proved more effective in reducing anti-emetic episodes, but also demonstrated a significantly diminished sedative effect[4]. This review suggests that pyridoxine-metoclopramide is considered a standard first-line therapy for HG, with secondary measures including promethazine and ondansetron. Administration of methyl-prednisolone alongside first- and second-line therapies should be considered, especially in severe cases of HG where rapid improvement is essential to avoid serious metabolic consequences leading to hospitalization.

REFERENCES

1. Davis M.
Nausea and Vomiting of Pregnancy.
J Perinat Neonat Nurs. 2004;18(4):312-28.

2. Sullivan C, et al.
A pilot study of intravenous ondansetron for hyperemesis gravidarum.
Am J Obstet Gynecol. 1996;174(5):1565-8.

3. Yost N, et al.
A Randomized, Placebo-Controlled Trial of Corticosteroids for Hyperemesis Due to Pregnancy.
Obstetrics and Gynecology 2003;102(6):1250-4.

4. Bsat F, et al.
Comparison of Three Outpatient Regimens in the Management of Nausea and Vomiting in Pregnancy.
Journal of Perinatology. 2003;23:531-5.

5. Safari H, et al.
The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: A randomized, double-blind, controlled study.
Am J Obstet Gynecol. 1998;179(4):921-4.