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Rapid efficacy of mirtazapine in the treatment of hyperemesis gravidarum with esophagus perforation and normoglycemic ketone positivity: a case report

Abstract

Hyperemesis gravidarum is a medical condition that may cause serious consequences for fetus and the mother. Treatment regimens are indeterminate in patients having severe and treatment-resistant conditions. Although antiemetics are known to be used for Hyperemesis Gravidarum in the literature, mirtazapine has been used effectively in some treatment-resistant cases. On the other hand, to the best of our knowledge, no reports on the efficacy of mirtazapine in cases of severe and treatment-resistant hyperemesis gravidarum have been reported in the literature. The aim of this study was to present a successful treatment with mirtazapine for a 28-year-old pregnant patient who developed esophageal perforation and Normoglycemic Ketone Positivity due to severe and treatment-resistant hyperemesis gravidarum. The study revealed that mirtazapine may be effective even in severe cases of hyperemesis gravidarum. In addition, the effectiveness of mirtazapine in the treatment of hyperemesis gravidarum was once again shown. However, the fact that mirtazapine may be used in the treatment of pregnant patients could be discussed.

Keywords: Mirtazapine, Hyperemesis Gravidarum, Severe Nausea, Esophagus Perforation, Normoglycemic Ketone Positivity.

Özofagus perforasyonu ve normoglisemik keton pozitifliği bulunan hiperemezis gravidarum tedavisinde mirtazapinin hızlı etkinliği: olgu sunumu

Özet

Hiperemezis gravidarum, fetus ve anne için ciddi sonuçlara neden olabilecek tıbbi bir durumdur. Şiddetli ve tedaviye dirençli olan hastalarda tedavi rejimleri belirsizdir. Antiemetiklerin literatürde hiperemezis gravidarum için kullanıldığı bilinmesine rağmen, mirtazapin bazı tedaviye dirençli vakalarda etkili bir şekilde kullanılmıştır. Diğer yandan, bildiğimiz kadarıyla, literatürde şiddetli ve tedaviye dirençli hiperemezis gravidarum vakalarında mirtazapinin etkinliği hakkında rapor bildirilmemiştir. Bu vakanın amacı, şiddetli ve tedaviye dirençli hiperemezis gravidarum nedeniyle özofagus perforasyonu ve normoglisemik keton pozitifliği gelişen 28 yaşında bir gebe hasta için mirtazapin ile başarılı tedavisini sunmaktır. Vaka mirtazapinin şiddetli hiperemezis gravidarum vakalarında bile etkili olabileceğini göstermiştir. Ek olarak, mirtazapinin hiperemezis gravidarum tedavisinde etkinliği bir kez daha gösterilmiştir. Bununla birlikte, mirtazapinin hamile hastaların tedavisinde kullanılabileceği gerçeği tartışılabilir.

Anahtar Kelimeler: Mirtazapin, Hiperemezis Gravidarum, Şiddetli Bulantı, Özofagus Perforasyonu, Normoglisemik Keton Pozitifliği.

Introduction

Mirtazapine is an orally administered tetracycline antidepressant increasing both noradrenergic and serotonergic activity (1, 2). It is frequently used in clinical practices especially for the treatment of depression and anxiety disorder since it is effective, potent and well tolerated (3). In addition, it has been reported that it can be used in the treatment of sleeping disorders, weight loss, and anorexia nervosa (1, 4). Furthermore, recent publications have indicated that mirtazapine can also be used with effective results in the treatment of nausea-vomiting (5, 6).

Hyperemesis gravidarum which is characterized by severe nausea and vomiting is a medical condition that can cause serious consequences for fetus and the mother (7, 8). It is estimated that nearly 78-89% of pregnant women experience hyperemesis gravidarum (8, 9). As a result various medical conditions such as dehydration, starvation, hospitalization, hypoglycemia, hypopotassemia and even esophagus perforation or medical abortion could be seen (7, 8). Nausea and vomiting during pregnancy are mostly believed to be related to either hormonal changes or psychological stress. It is necessary to exclude other organic causes of vomiting before diagnosis (8). Since the pathophysiology of nausea and vomiting in pregnancy is not clear, there is no scientific treatment for its causes. Treatments are usually intended to relieve the symptoms during that period. Application of anti-emetics with liquid-electrolyte and vitamin supplements is the first option in order to avoid negative consequences (10). Other treatment options accommodate a wide range from antiemetic drugs to psychotherapies (11). In addition, the number of publications reporting that mirtazapine is effectively used in the treatment of hyperemesis gravidarum is not very rare (2, 12, 13). However, to the best of our knowledge, there is no report revealing the efficacy of mirtazapine in cases of hyperemesis gravidarum with esophagus perforation.

A successful treatment with mirtazapine in a 28-year-old woman who experienced esophageal perforation due to the treatment-resistant hyperemesis gravidarum is presented in the study.

Case Report

A 28-year old patient had gravida 4 and parity 3. She was a high school graduate housewife. The patient was admitted to our hospital, obstetric clinic with the complaints of severe nausea and vomiting. She had many abdominal cramps and could not stand them anymore. After the examination, diagnosis was esophageal perforation and its treatment was initiated accordingly. The patient had symptoms of minor depression and anxiety before the pregnancy. In the second week of pregnancy, the complaints of nausea and vomiting started, and she was diagnosed with hyperemesis gravidarum at the sixth week. Prokinetics including 8 mg/d of ondansetron, 8 mg/d mg of prednisolone, and 10 mg/d of metoclopramide were administered for over 1 month. However, there was no relief for nausea, and vomiting. The patient had a weight loss of 8.5 kg compared to the pre-pregnancy by the 8th week. 'normoglycemic ketone positivity was present in the urine test. During pregnancy, the patient's social and familial stressors were formed and the complaints of hyperemesis gravidarum increased. Medical abortion was planned because the patient and the vitals of the baby got worse. . The patient was finally consulted to a psychiatry clinic. After a detailed history and psychological examination, the patient was not diagnosed psychopathology according to the DSM-5 diagnostic criteria. The patient was recommended to use mirtazapine. The patient was able to tolerate food and beverages for the first time in two hours after receiving the first 15 mg of mirtazapine. A week later, the complaints of nausea and vomiting decreased significantly. Oral mirtazapine treatment was continued for 60 days. After the termination of mirtazapine treatment, the nausea level was tolerable for the patient. The fetus

was within the normal limits on monthly ultrasonography control examinations while using mirtazapine and after discontinuation. Mother's weight gain was normal. She gave birth with vaginal delivery at 38 weeks of gestation. The baby's weight, height and head circumference were within normal percentile values. There were no diseases. Feeding of the baby was sufficient. There was no birth complication for the mother. She had no complaints during follow-up after delivery.

Discussion

Hyperemesis gravidarum is a condition characterized by severe nausea and vomiting in pregnant women and the treatment protocol is still not clear. The successful treatment of a patient having severe hyperemesis gravidarum with normoglycemic ketone positivity and esophageal perforation with mirtazapine was presented in our study. We believe that our case is a significant study because of the fact that the normoglycemic ketone positivity and esophageal perforation even proposed medical abortion are so severity hyperemesis gravidarum and show very fast responsivity.

Although nausea and vomiting during pregnancy are considered to be a normal part of the process, symptoms ranging from women's displeasure to medical abortion may occur (9). Therefore, dehydration, starvation, hospitalization, hypoglycemia, hypopotassemia, or even esophagus perforation or medical abortion may be experienced. However, these symptoms are known to vary individually (7). In our study, despite there were many different treatments in the literature, we used the treatment of mirtazapine, being an antidepressant for a very severe hyperemesis gravidarum case. Our patient benefited from mirtazapine treatment according to the previous reports (2, 13-15). The reason for choosing mirtazapine in our patient was that it was shown to be effective on hyperemesis gravidarum in the relevant literature (2, 13-15). Nevertheless, the fact that we differentiated our case from previous cases

was the presence of relatively severe case indicators such as the development of esophageal perforation and normoglycemic ketone positivity, and the suggestion of medical abortion. However, we think that the patient's symptoms are regressed faster than expected with mirtazapine. The most likely mechanism of action for a successful treatment of hyperemesis gravidarum with mirtazapine may be the fact that the blocks 5HT₃ receptor, such as Ondansetron is an antiemetic (16, 17).

Another reason for choosing mirtazapine in our case was that mirtazapine did not cause any intrauterine fetal loss after the first trimester. There was no risk of teratogenicity and there was no developmental difference when compared to the controls (12). Another reason is that mirtazapine may have therapeutic effects on the psychic effects of pregnancy and hyperemesis gravidarum (14). Ondansetron tested in our patient with 5HT₃ receptor blockade was ineffective for hyperemesis gravidarum whereas mirtazapine was found to be effective. Psychological factors such as anxiety and depression may play a role in the pathogenesis and prevention of hyperemesis. Therefore, considering the effect of psychological factors in the treatment of hyperemesis, mirtazapine with additional 5-HT_{1a}-stimulation may be selected to outperform selective 5HT₃-receptors (18).

Conclusion

In conclusion, our study showed that mirtazapine may be effective even in cases of severe hyperemesis gravidarum. In addition, the effectiveness of mirtazapine in the treatment of hyperemesis gravidarum was to be shown once again. However, it could be discussed that mirtazapine may be used in the treatment of pregnant patients. Clinicians should be aware that mirtazapine is an important alternative in the treatment of disorders such as hyperemesis gravidarum during pregnancy and anxiety and depressive disorder in daily practice. A

prospective design, larger sample and longitudinal studies will be beneficial in terms of revealing the safety of mirtazapine.

Informed Consent: Written informed consent was obtained from the patient.

Conflict of Interest: The authors declared no conflict of interest.

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References

1. De Boer T, Nefkens F, Van Helvoirt A, Van Delft A. Differences in modulation of noradrenergic and serotonergic transmission by the alpha-2 adrenoceptor antagonists, mirtazapine, mianserin and idazoxan. *J Pharmacol Exp Ther* 1996;277:852-860.
2. Guclu S, Gol M, Dogan E, Saygili U. Mirtazapine use in resistant hyperemesis gravidarum: report of three cases and review of the literature. *Arch Gynecol Obstet* 2005;272:298-300.
3. Özçankaya R, Acar A. A comparison of amitriptyline and mirtazapine side effects in depression treatment. *Bull Clin Psychopharmacol* 2001;11:17-27.
4. Hrdlicka M, Beranova I, Zamecnikova R, Urbanek T. Mirtazapine in the treatment of adolescent anorexia nervosa. *Eur Child Adolesc Psychiatry* 2008;17:187-189.
5. Pae C-U. Low-dose mirtazapine may be successful treatment option for severe nausea and vomiting. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:1143-1145.
6. Kim S-w, Shin I-s, Kim J-m, Kang H-c, Mun J-u, Yang S-j, J Yoon. Mirtazapine for severe gastroparesis unresponsive to conventional prokinetic treatment. *Psychosomatics* 2006;47:440-442.
7. Şimşek Y, Çelik Ö, Yılmaz E, Karaer A, Yıldırım E, Yoloğlu S. Assessment of anxiety and depression levels of pregnant women with hyperemesis gravidarum in a case-control study. *J Turk Ger Gynecol Assoc* 2012;13:32.

8. Kender EE, Yuksel G, Ger C, Ozer U. Eating attitudes, depression and anxiety levels of patients with hyperemesis gravidarum hospitalized in an obstetrics and gynecology clinic. *Dusunen Adam The Journal of Psychiatry and Neurological Sciences* 2015;28:119-126.
9. Chan RL, Olshan AF, Savitz DA, Herring AH, Daniels JL, Peterson HB, et al. Maternal influences on nausea and vomiting in early pregnancy. *Matern Child Health J* 2011;15:122-127.
10. Büyükkurt S, Demir SC, Özgünen FT, Evrücke İC, Kadayifci O, Güzel AB. Evaluation and Treatment of the Patients with Nausea and Vomiting in Pregnancy: Review. *Turkiye Klinikleri J Gynecol Obst* 2008;18:106-116.
11. Kavakci O, Yenicesu GI. Eye movement desensitization and reprocessing [EMDR] for hyperemesis gravidarum: a case series. *Dusunen Adam The Journal of Psychiatry and Neurological Sciences* 2014;27:335-341.
12. Saks B. Mirtazapine: treatment of depression, anxiety, and hyperemesis gravidarum in the pregnant patient. A report of 7 cases. *Arch Womens Ment Health* 2001;3:165-170.
13. Naguy A. Mirtazapine for Major Depression Developed After Hyperemesis Gravidarum. *Am J Ther* 2019.
14. Rohde A, Dembinski J, Dorn C. Mirtazapine [Remergil] for treatment resistant hyperemesis gravidarum: rescue of a twin pregnancy. *Arch Gynecol Obstet* 2003;268:219-221.
15. Uguz F. Low-dose mirtazapine in treatment of major depression developed following severe nausea and vomiting during pregnancy: two cases. *Gen Hosp Psychiatry* 2014;36:125.
16. Montgomery S. Safety of mirtazapine: a review. *Int Clin Psychopharmacol* 1995;10:37-45.

17. Theobald DE, Kirsh KL, Holtsclaw E, Donaghy K, Passik SD. An open-label, crossover trial of mirtazapine [15 and 30 mg] in cancer patients with pain and other distressing symptoms. *J Pain Symptom Manag* 2002;23:442-447.
18. Schwarzer V, Heep A, Gembruch U, Rohde A. Treatment resistant hyperemesis gravidarum in a patient with type 1 diabetes mellitus: neonatal withdrawal symptoms after successful antiemetic therapy with mirtazapine. *Archives of gynecology and obstetrics* 2008;277:67-9.