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Treatment of hyperemesis gravidarum with the 5-HT_3 antagonist ondansetron (Zofran)

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Summary
Ondansetron is a 5-hydroxytryptamine receptor antagonist which is known to be a highly effective anti-emetic drug for chemotherapy-associated nausea and vomiting and for postoperative nausea. We report here a case where ondansetron was used in severe hyperemesis gravidarum to avoid parenteral nutrition. The drug was used intermittently in every trimester with no apparent adverse effects on mother or infant.

Keywords: hyperemesis gravidarum, ondansetron, 5-hydroxytryptamine receptor

A 29-year-old woman presented at eight weeks gestation in her first pregnancy with nausea and vomiting and a weight loss of 3.5 kg. On admission she was clinically dehydrated and tachycardic, although there was no ketonuria. Intravenous fluid replacement was commenced together with intramuscular promethazine (Phenergan) for nausea. An ultrasound scan confirmed a singleton pregnancy of the same gestation. Two days after admission the vomiting was unrelieved and so intramuscular prochlorperazine (Stemetil) was added to the regime. (Rectal therapy was refused by the patient.) This combination did not relieve her symptoms and she remained on intravenous fluids, unable to tolerate any oral intake. Potassium chloride supplementation was required to correct hypokalaemia of 2.9 mmol/l. On the 14th day of admission intramuscular metoclopramide (Maxalon) was added with gradual relief of her symptoms over the following seven days. She was then discharged on oral metoclopramide.

At 12 weeks gestation the patient was readmitted with worsening recurrent nausea and vomiting which failed to respond to any of the drugs previously used. She was again dehydrated and tachycardiac on admission and urinalysis revealed moderate ketonuria (2+ on ward dipstick testing). She had lost 10 kg in weight (20% of the pre-pregnancy weight). Intravenous fluid replacement was recommenced. The patient and her partner were unwilling to consider termination of pregnancy or parenteral nutrition. After 14 days with no relief from vomiting, ondansetron (Zofran) 8 mg intravenously twice daily was commenced resulting in dramatic cessation of vomiting after a single dose although the nausea persisted. She was able to tolerate a light diet and oral therapy two days later and was well enough to be discharged 14 days after admission, taking ondansetron 4 mg tid orally.

At formal antenatal booking two weeks later she was still nauseated. The vomiting was controlled on an oral dose of ondansetron

Ondansetron (Zofran)

Uses
- management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy
- prevention and treatment of postoperative nausea and vomiting

Mode of action
- highly selective 5-HT_3-receptor antagonist
- precise mode of action not known, but 5-HT_3 receptors are present in vagal afferents from the small intestine and in the floor of the fourth ventricle
- mode of action probably by antagonism of the receptors in both central and peripheral sites

Side-effects
- constipation, headaches, flushing/sensation of warmth of the head and epigastrium
- transient disturbances of liver aminotransferases
- rarely, hypersensitivity reactions, visual disturbances, chest pain, cardiac arrhythmias

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4 mg tid. Throughout the rest of her pregnancy she remained nauseated but any vomiting was controlled with oral ondansetron. The patient self-medicated on an intermittent basis once or twice daily. Whenever treatment was stopped the patient experienced a recurrence of vomiting. She was able to eat enough to maintain her body weight and finally discontinued therapy at 33 weeks gestation. She still had occasional episodes of vomiting and the nausea persisted throughout her pregnancy. She went into labour spontaneously at 39 weeks gestation and was delivered of a healthy male infant weighing 2.7 kg with no detectable abnormality. At her postnatal check, she was in good health with resolution of her vomiting and the baby remained well.

Discussion

This case reports the use of ondansetron from 14 weeks to 33 weeks gestation in a primigravida to control severe hyperemesis which was refractory to conventional treatments. The patient had lost 20% of her pre-pregnancy weight and was unable to tolerate any oral fluid. The potential theoretical risks of this drug treatment were clearly understood by the patient and her partner. The anti-emetic effect of ondansetron was dramatic in its rapidity of action and its efficacy in preventing further vomiting.

The literature contains only two brief references to the use of ondansetron in pregnancy. In the first, the drug was used for two weeks in the first trimester in a patient with severe hyperemesis leading to weight loss and dehydration.[1] The patient's condition did not recur following cessation of drug, and a healthy infant was born at term. The second report involved the use of ondansetron to control nausea in a patient with renal disease in pregnancy.[2] The drug was used for three weeks during the third trimester and no adverse effect was seen in the infant.

Summary points

- hyperemesis gravidarum can be a life-threatening condition
- standard anti-emetic drugs are often of limited efficacy
- ondansetron appears to be an effective treatment in hyperemesis gravidarum
- further information from larger studies will be needed before widespread use of ondansetron in pregnancy can be recommended

Ondansetron is a 5-hydroxytryptamine (5-HT) antagonist with action specific for the 5-HT receptors within the peripheral and central nervous system (5-HT_3 receptors).[3] The main action of the drug is within the central nervous system[3] although it does also increase gastric emptying.[4] The drug is highly effective at reducing the emetic side-effects of chemotherapy[5] or radiotherapy[6] and is also effective at reducing postoperative nausea and vomiting.[7] Extensive premarketing tests showed that ondansetron had a wide therapeutic index, no interaction with commonly prescribed drugs and minimal side-effects.[4]

The paucity of data on the use of ondansetron in pregnancy make it difficult to be certain of the safety of the drug in pregnancy. This report describes the longest published duration of use of ondansetron from the second trimester through to the third without any adverse clinical effects. The possibility of a late adverse effect upon foetal and infant development cannot be ruled out at this time, and it is not possible to make any comment as to the safety of the drug if used early in the first trimester during organogenesis. However, the general safety of the drug and the evidence from the cases now reported indicate that ondansetron may have a role in the management of the patient with severe, refractory hyperemesis which persists beyond the first trimester.

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