INTRODUCTION

Ondansetron (Zofran® - GlaxoSmithKline) is currently approved for prevention and treatment of chemotherapy-induced emesis, specifically with highly emetogenic regimens such as high-dose cisplatin. It is also used commonly to prevent post-operative nausea and vomiting. The chemical compound is 1,2,3,9-tetrahydro-9-methyl-3-[3-(3-methyl-1 H-imidazol-1-yl)] methyl carbazol-4-one hydrochloride dihydrate and is a racemic mixture with a molecular weight of 366 Daltons. The molecular formula is C18-H19-N3-O-HCl-2H2O. There are several related compounds available including dolasetron, granisetron, tropisetron, and alosetron; none of them have been as well studied or are as widely used as ondansetron. Since its introduction, ondansetron has gained popularity as a treatment for nausea due to its effectiveness and low incidence of complications. With concerns having been raised about the arrhythmogenic potential of some anti-emetics in the antipsychotic class (i.e. droperidol), and a supply shortage of others (i.e. intravenous prochlorperazine), the use of ondansetron will likely increase.

PHARMACOLOGY

Ondansetron is available as an intravenous solution in concentrations of 2 mg/ml, 4 mg/5 ml, and 32 mg/50ml. The injectable formulation should be diluted in 30 ml of 3% dextrose injection or in 0.9% sodium chloride injection before administration. It is unstable in an alkaline environment and will precipitate in IV tubing; therefore, the access line should be flushed before and after intravenous infusion. Subcutaneous infusion has been reported. This mode of delivery, however, is not recommended by the manufacturer due to the product’s acidic pH of 3.5. Suggested doses are given as an intravenous drip over 15 minutes. Tablets are also available (4mg, 8mg, 24mg), as are rapidly dissolving tablets (4mg, 8mg) and an oral solution (4mg/5cc). Ondansetron was approved in the United States in 1991 for the prevention and treatment of chemotherapy-induced emesis. Best results have been seen when ondansetron is used in conjunction with highly emetogenic chemotherapeutic regimes like high-dose cisplatin. It is also effective, though less so, with moderately emetogenic regimes. In addition, it is approved for the prevention and treatment of post-operative nausea and vomiting. Recently, ondansetron has been used to treat emesis from a variety of causes. Case reports describe success in reducing vomiting associated with radiation therapy, pregnancy, aceamphenon and theophylline overdoses, terminal cancer, as well as reducing the symptoms of the carcinoid and irritable bowel syndrome. More recently it has been studied as a treatment for symptomatic gastroenteritis in children with success. Ondansetron is considered to be a pregnancy class B because it appears to be safe in animal studies but no human studies have been done. Ondansetron is excreted in breast milk, albeit its safety in lactation has not been established.

MECHANISM OF ACTION

Ondansetron is a selective serotonin 5-HT3 receptor antagonist. It is thought to function by blocking serotonin receptors on both visceral afferent nerves in the gastrointestinal tract and neurons in the chemoreceptor trigger zone in the area postrema of the medulla oblongata (the vomiting center). During chemotherapy or radiotherapy, there is cellular damage in the intestinal tract that results in the release of serotonin from enterochromaffin cells. The antagonism of peripheral serotonin receptors on intestinal afferents not only causes acetylcholine release with a subsequent decrease in gastrointestinal mobility but also decreases vagal afferrent stimulation to the brainstem. Thus, inhibition of serotonin receptors is thought to suppress nausea and vomiting by three different, but linked, mechanisms.

PHARMACOKINETICS

The oral bioavailability of ondansetron is 56-60% with peak plasma concentrations in approximately 1.0 to 1.5 hours. Protein binding is 70-76%, and the volume of distribution is 1.8 L/kg (163 L). The combination of these two factors limits the potential effectiveness of hemodialysis in overdose.

Elimination is predominantly by hepatic metabolism; hydroxylation is followed by glucuronidation or sulfate conjugation. While ondansetron itself does not induce or inhibit the cytochrome P450 system, it is metabolized by these enzymes. Therefore, drugs that alter the activity of the cytochrome P450 system may affect the pharmacokinetics of Ondansetron. Only about 5-10% of a given dose is excreted unchanged in the urine. Ondansetron is excreted in the gastrointestinal tract as well. One study reported approximately 25% of an intravenous dose in the feces. Plasma half-life is 3.0-3.5 hours. Plasma clearance is 600 mL/min, while renal clearance is only 20 mL/min.

For the prevention of chemotherapy-induced nausea, the dose is 32 mg IV or 0.15 mg/kg over 15 minutes. For children, the loading dose is 5mg/m2/dose followed by 0.15 mg/kg every eight hours. It is given 30 minutes prior to the start of chemotherapy, then four and eight hours later. For the prevention of post-operative nausea the dose is 4 mg (0.15 mg/kg in children) IV over 2-5 minutes or 16 mg PO given 1 hour prior to anesthesia. For prevention or treatment of radiotherapy-induced nausea, the dose is 8mg PO three times a day. For other indications, such as acenomphen toxicity, a typical starting dose for an adult is 4-8 mg.

TOXICOLOGY

In therapeutic doses, ondansetron has relatively few side effects. One of the most common of these side effects is constipation, occurring in 16% of patients in one study. In another study, 10 of 67 (15%) patients complained of constipation. Other prevalent reactions include headache (17-26%), a warm or flushed sensation, and diarrhoea; these effects, though, do not appear
to occur with greater frequency than with placebo.
A mild elevation in hepatic transaminases (less than twice normal) has been reported in 6-17% of patients receiving ondansetron. However, other studies report that these changes may be attributable to concomitant chemotherapy, and not ondansetron itself. One case of hepatic failure has been reported in a patient receiving ondansetron. Of note, this patient also had viral hepatitis and lymphoma, leaving the precise etiology of hepatic failure uncertain. While extrapyramidal effects such as dystonia or akathisia are common side effects with other antiemetics including phenothiazines and butyrophenones, they appear only rarely with ondansetron. Three cases of extrapyramidal effects have been reported. Sedation, which is also seen with other antiemetics, is reported infrequently with ondansetron.
Seizures have been reported in as many as 1% of patients receiving ondansetron. However, only one case of seizure has been reported in a patient without brain metastasis, severe metabolic derangement, or anti-neoplastic therapy.
There are 24 reported cases of anaphylactic or anaphylactoid reactions involving urticaria, hypotension, angioedema, or bronchospasm. One case of fatal anaphylactic shock has been reported. Because many patients receiving ondansetron are also receiving chemotherapeutic agents, radiotherapy, or other medications with significant side effects, and many have metastatic disease, it difficult to quantify the contribution of ondansetron to these adverse effects. For example, in the study by Smith, 16% of patients experienced constipation, but in only 5% was the constipation felt to be "almost certainly or probably linked to ondansetron." Overdose is rare and no fatal dose has been established. The largest single dose reported was 145 mg (1.5 mg/kg). This patient experienced hot flashes, and warm skin hyperesthesia, and a transient increase in his lactate dehydrogenase. A second case report describes the largest daily dose was 252 mg, given in three 84 mg (1.5 mg/kg) doses 2 hours apart. This patient also experienced hot flashes, as well as a pruritic sensation of the nose and a feeling of restlessness. Both patients recovered without sequelae.
Treatment after an ondansetron overdose is primarily supportive. Attention to the patient’s airway, breathing, and circulation is paramount. Intubation could be necessary if other sedating co-ingestions potentiates act synergistically with ondansetron. Activated charcoal should be used for gastrointestinal decontamination. The side effects of constipation, seizures, and anaphylaxis are treated by conventional standard.

SUMMARY

Ondansetron is a selective serotonin 5-HT3 receptor antagonist approved for the prevention and treatment of chemotherapy-induced emesis and post-operative nausea. Its use is increasing, nonetheless, with the potential decreased availability of other antiemetics. Ondansetron appears to have a wide therapeutic index with mild side effects that occur infrequently. Side effects that are common with phenothiazines and butyrophenones are rare with ondansetron. Toxicity has been minimal even when 10 times the recommended dose has been given. Therefore, regardless of etiology, ondansetron continues to be a safe useful adjunct in treating those patients with vomiting.

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