Ondansetron: A Selective 5-HT₃ Receptor Antagonist and Its Applications in CNS-Related Disorders

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ABSTRACT

Ondansetron is a selective 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist that has been introduced to clinical practice as an antiemetic for cancer treatment-induced and anesthesia-related nausea and vomiting. Its use under these circumstances is both prophylactic and therapeutic. It has a superior efficacy, safety and pharmaco-economic profile compared with other groups of antiemetics, namely antidopaminergics, antihistamines and anticholinergics. However, its place in the management of anticipatory and delayed vomiting in cancer treatment and as a rescue antiemetic in surgical patients needs to be further explored. Furthermore, recent animal and human research also reflects its possible novel application in the treatment of other disease states, such as alcoholism, cocaine addiction, opioid withdrawal syndrome, anxiety disorders, gastrointestinal motility disorders, Tourette's syndrome and pruritus. This review revisits the widespread physiological and pathological effects of 5-HT and discusses both the basic science literature and the clinical developments responsible for the conventional and novel uses of ondansetron. In addition, new discoveries relating to the effects of ondansetron on other receptors/channels and their possible therapeutic applications are presented.

INTRODUCTION

Ondansetron, a selective antagonist of 5-hydroxytryptamine₃ (5-HT₃, serotonin₃) receptor subtype, has been the therapy of choice for nausea and vomiting evoked by chemotherapy, radiotherapy, anesthesia or surgery since it was clinically introduced. In addition,

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ondansetron is used in nausea and vomiting elicited by drug overdose or poisoning, as an antidepressant, and to ameliorate pruritus, irritable bowel syndrome, diarrhea associated with cryptosporidiosis or diabetes, chronic refractory diarrhea, certain pain states, alcohol dependency, opiate withdrawal, vertigo, cerebellar tremor and Parkinson's disease treatment-related psychosis. Ondansetron is well tolerated and its side effects are mild. The studies on the use of ondansetron in new indications continue. Given this plethora of research activity, we found it necessary to focus our review on a subset of recent papers. We elected to cover only new findings on its pharmacological and toxicological properties, mainly concerning its use in central nervous system (CNS) — related disorders.

PHARMACOLOGY

The 5-HT₃ Receptor

5-Hydroxytryptamine (5-HT, serotonin) is a monoaminergic neurotransmitter that modulates numerous neuronal functions (48), and has been implicated in the etiology of many disease states. 5-HT may be particularly important in mental illness, such as depression, anxiety, schizophrenia, eating disorders, obsessive compulsive disorder, panic disorders and migraines.

In terms of physiological functions, 5-HT helps modulate the contraction and relaxation of smooth muscles in the respiratory and gastrointestinal tracts and blood vessels, platelet plug formation during hemostasis, provocation of pain, induction of vomiting, precipitation of mood changes and induction of sleep (15). 5-HT produces its physiological effects by interacting with various 5-HT receptor subtypes that are classified as 5-HT₁₋₇ (26).

Of greater relevance to this review is the 5-HT₃ receptor, a serotonin-gated ion channel selectively permeable to Na⁺, K⁺, and Ca²⁺ ions, which are involved in the process of depolarization. The range of ondansetron effects in different disorders may be attributed to the wide distribution of 5-HT₃ receptors and their various roles in many organs. High concentrations of 5-HT₃ receptors are found in the central nervous system (CNS) in the area postrema (chemoreceptor trigger zone), nucleus tractus solitarius (vomiting center), substantia gelatinosa (at all levels), nuclei of the lower brain stems, such as the trigeminal nucleus and the dorsal vagal complex, and in the spinal cord (12). In addition, 5-HT₃ receptors are found at lower densities in the cerebral cortex, hippocampus, amygdala and medial habenula (26). Peripherally, they are on the visceral, autonomic and sensory nerves, pre- and postganglionic autonomic neurons, as well as enterochromaffin cells.

5-HT₃ receptors are implicated in many brain functions, and play critical roles in many physiological and pathological processes, some of which are serotonin-mediated. These include vasomotor reflexes, control of gastrointestinal function, pain mechanisms, cardiovascular regulation, neuronal function, and limbic-cortical functioning (47). In addition, 5-HT₃ receptors are linked with several other neurotransmitters, including norepinephrine, acetylcholine, cholecystokinin, γ -aminobutyric acid (GABA), glycine, and dopamine (20,71,73).

Mechanism of Action

The antagonistic properties of ondansetron at the 5-HT₃ receptors have been examined using rat isolated neuronal preparations and the Bezold–Jarisch reflex response in the anesthetized cats and rats (15). Ondansetron is a potent, highly selective, competitive antagonist at 5-HT₃ receptors. It demonstrates some affinity to other receptor subtypes, including 5-HT_{1B}, 5-HT_{1C}, 5-HT₄, opioid, and α_1 -adrenergic receptors (20). However, ondansetron has 1000:1 selectivity toward 5-HT₃ receptors (15).

Ondansetron acts on the CNS as well as on the peripheral nervous system (PNS). While all mechanisms of ondansetron's effects are not fully understood, it clearly lacks dopamine receptor antagonist property. Ondansetron is likely to inhibit 5-HT₃ receptors in CNS regions (including the area postrema, nucleus tractus solitarius, amygdala and dorsal raphe nucleus) and, through 5-HT₃ receptor antagonism, it appears to inhibit dopamine release/cell firing in nucleus accumbens. In the PNS, ondansetron also inhibits 5-HT₃ receptors, thereby blocking the depolarization of vagal afferent nerves and the myenteric neurons, leading to an attenuation of 5-HT₃ receptor-mediated nociceptive response (15).

PHARMACOKINETICS

Ondansetron is available both for oral and intravenous administration. In both preparations it is present as a hydrochloride dihydrate base. The oral preparation can be co-administered with food or antacids without any significant effect on absorption. The intravenous preparation is an isotonic aqueous solution that has been buffered to a pH of 3.5 with sodium citrate and citric acid monohydrate. It is administered either by slow intravenous injection or by intravenous infusion over a period of minutes (75).

The bioavailability of orally administered ondansetron is only 60%. The low bioavailability is due to a significant first-pass metabolism. The peak plasma concentration of ondansetron is usually reached at approximately 1.5 h after oral administration. A major portion of this drug, about 75%, is bound to plasma proteins. It has a large volume of distribution, approximately 160 L. The cerebrospinal fluid concentration of ondansetron is less than 15% of its plasma concentration. Ninety-five percent of the administered drug is metabolized by phase I hydroxylation, followed by phase II conjugation with glucuronic acid and sulfates in the liver. It has been shown that cytochromes P450 1A2, 2D6, and 3A are involved in the phase I hydroxylation of ondansetron (70). The inactive metabolites are excreted in urine and feces. Clearance of the drug occurs at the rate of 541 mL/min, resulting in a terminal elimination half-life of 2 to 4 h. The clearance rate is slower in females and the elderly, but this difference is not believed to be of any clinical relevance (59). The pharmacokinetics of ondansetron in children appears to be similar to that in adults. In patients with moderate to severe hepatic dysfunction a reduction in ondansetron dose is recommended, especially when the drug is used at progressively higher doses over a period of time, as in cancer treatment (76).

ANTIEMETIC PROPERTY

The antiemetic effects of ondansetron have been demonstrated in ferrets. Ondansetron prevented retching and vomiting induced by cisplatin (19), cyclophosphamide, or X-radiation (1,63). At a low dose (0.01 mg/kg s.c.), ondansetron significantly delayed the onset of emesis and markedly reduced the number of retches and vomits caused by cisplatin; at 0.1 mg/kg the emetic response was abolished. At 0.5 mg/kg s.c. ondansetron abolished vomiting and markedly reduced retching due to cyclophosphamide. At the same dose it abolished retching and vomiting caused by X-radiation. In other experiments ondansetron, 0.5 mg/kg s.c., arrested X-radiation-induced vomiting. It has not been definitively established whether ondansetron's antiemetic action in chemotherapy-induced emesis is centrally or peripherally mediated. Cytotoxic chemotherapy appears to be associated with the release of serotonin from the enterochromaffin cells of the small intestine. This released serotonin may stimulate the vagal afferents through the 5-HT₃ receptors and initiate the vomiting reflex (25).

Ondansetron vs. Other 5-HT₃ Antagonists

In addition to ondansetron, three other 5-HT₃ antagonists: granisetron, dolasetron, and tropisetron, are currently available for clinical use. While granisetron, dolasetron and its major metabolite are pure 5-HT₃ antagonists, ondansetron and tropisetron are also weak antagonists at 5-HT₄ receptors. Ondansetron has also some affinity for other serotonin receptor subtypes and to the μ -opioid receptor. Despite some design shortcomings in the clinical trials conducted to directly compare the 5-HT₃ antagonists, most studies show that their antiemetic activity (prevention of cisplatin-induced emesis) and tolerability are almost identical for the four antagonists. The four drugs are also equally effective in the prevention of chemotherapy-induced emesis. Their side effects are mild and infrequent (24,56).

Ondansetron vs. other Antiemetic Drugs

A study comparing the prophylactic antiemetic effect of ondansetron (4 mg, i.v.) with that of droperidol (20 mg/kg, i.v.) was conducted on 158 women undergoing outpatient gynecologic laparoscopy under anesthesia. Based on the number of women who experienced postoperative nausea and vomiting as well as on the level of sedation, there was no difference between the two drugs (62). Another comparative, randomized, double-blind study was conducted on 60 adults requiring elective supratentorial craniotomy. The patients received standardized intravenous anesthesia with 4 mg of ondansetron, 0.625 mg of droperidol, or placebo at the skin closure. This study showed that both ondansetron and droperidol are effective in reducing nausea, and that droperidol is particularly effective in reducing vomiting. Neither drug caused more sedation than placebo (22).

In a double-blind, randomized study involving 51 female patients undergoing gynecological diagnostic laparoscopy, the postoperative nausea score was lower in patients receiving a combination of ondansetron (4 mg, i.v.) and dexamethasone (8 mg, i.v.) than ondansetron alone (4 mg, i.v.) (53).

In the prevention of perioperative nausea during cesarean delivery under spinal anesthesia intrathecal fentanyl, 20 mg, has been found to be superior to intravenous ondansetron, 4 mg. The superiority of ondansetron was demonstrated in a double-blind study on 30 healthy patients randomized to receive either intrathecal fentanyl or intravenous ondansetron (38).

THERAPEUTIC USE

Iatrogenic nausea and vomiting has plagued mankind from the time the practice of medicine was introduced. Chemotherapy, radiation treatment, anesthesia and surgery contribute greatly to this side effect. Nausea is diminishing quality of life, while vomiting causes substantial pathophysiological aberrations, including dehydration, metabolic alkalosis, esophageal tears and interference with wound healing following surgery (20).

In the past, medical therapy-related vomiting was preventable with only moderate success, using antihistamines, anticholinergics and dopamine receptor antagonists. Patient compliance suffered in view of associated side effects that included sedation, dry mouth, and extrapyramidal dyskinesia (18,47). The delineation of 5-HT receptor subtypes by the scientists and the subsequent discovery of 5-HT₃ receptor selective antagonists has contributed to more favorable treatment outcomes in cancer patients seeking chemotherapy or radiation treatment (24,63) and, because of fewer side effects, to an improvement in patient compliance. Moreover, the introduction of 5-HT₃ antagonists to anesthesiological practice has made postoperative recovery more comfortable (35) and cost-effective (67,69). The most recent clinical studies demonstrate that 5-HT₃ antagonists can significantly reduce the incidence of nausea in breast cancer patients receiving moderately emetogenic chemotherapy and should be employed in this setting (49). Ondansetron was the first 5-HT₃ antagonist introduced into clinical practice; others, including granisetron, tropisetron and dolasetron, followed in rapid succession.

Nausea and Vomiting

Drug-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting. Chemotherapeutic agents, by their inherent cytotoxic effect, cause the release of 5-HT from enterochromaffin cells of the intestine; the resultant stimulation of the vagus nerve induces vomiting. This has been demonstrated in animal models treated with a potent emetogenic chemotherapeutic agent, cisplatin (2). Preemptive surgical vagotomy or pharmacological 5-HT₃ blockade, effectively prevented cisplatin-induced emesis in ferrets (3). Furthermore, it has been established in several randomized, double-blind, comparative trials that a 5-HT₃-receptor antagonist alone is more effective than metoclopramide and equal to or better than the combination of metoclopramide and dexamethasone in prevention of cisplatin-associated emesis (20).

Ondansetron, being a 5-HT₃-receptor antagonist, was introduced into clinical practice as an antiemetic. Many randomized multicenter comparative studies demonstrated greater efficacy and safety of ondansetron as compared to its predecessor, metoclopramide (14).

In these trials, fewer patients in the ondansetron group exhibited vomiting, and, those that did, had reduced numbers of episodes, compared with the metoclopramide group (39). However, in a recent study of 24 patients receiving high-dose chemotherapy with bone marrow transplantation, ondansetron (0.15 mg/kg as a continuous infusion every 12 h starting on the first day of chemotherapy) had poor antiemetic efficacy. During the first 3 days of therapy ondansetron failed to prevent emesis in twenty-three (96%) of patients. Fortunately, in patients undergoing organ transplantation appropriate doses of 5-HT₃-receptor antagonists with phenothiazine and corticosteroids were shown to improve the safety and efficacy of antiemetic regimens (49).

Ondansetron is usually administered orally for prophylaxis and treatment of chemotherapy-induced vomiting. Currently, oral preparations are marketed as tablets, oral disintegrating tablets and fruit-flavored syrup. Intractable vomiting, a rare event, is treated with intravenous infusion of ondansetron.

Opioid-induced emesis. The antiemetic efficacy of ondansetron in nausea and vomiting, caused by opioids, was studied in a randomized double-blind, placebo-controlled study involving 520 patients (317 females, 203 males). Significantly more patients who received ondansetron (8 or 16 mg i.v.) were satisfied or very satisfied with their antiemetic treatment than those who received placebo (64). In a double-blind, randomized, parallel-group study of 1366 patients who experienced opioid-induced emesis, ondansetron (8 mg or 16 mg i.v.) was significantly better than metoclopramide 10 mg ($P < 0.05$) in complete control of emesis or nausea as well as in other parameters of efficacy (17).

Radiation treatment-induced nausea and vomiting

Total body irradiation and focal irradiation aimed at the upper abdomen induce the release of 5-HT due to the damage they cause to enterochromaffin cells of the small intestine (21). Randomized multicenter studies compared ondansetron with metoclopramide and have shown the superior efficacy of ondansetron in the prevention of radiation-related emesis (52). In some studies, however, the statistical significance of this efficacy lasted only through the first few days following radiation treatment. This might be due to an overall low incidence of vomiting three days post-radiation and/or to the small sample size.

Postoperative nausea and vomiting

Postoperative nausea and vomiting is one of the causes of post-surgical morbidity. It is, therefore, a significant 'fear-factor' in patients presenting for operations. Postoperative vomiting is caused by the central effect of anesthetic agents stimulating the chemoreceptor trigger zone as well as by the peripheral effect of surgical manipulation of the intestines and diffusion of nitrous oxide into the intestinal lumen (14). In addition, the upper airway manipulation during tracheal intubation can contribute to this insult on the vomiting center. As in chemotherapy and radiation treatment, many randomized, double-blind, controlled studies dealt with anesthesia- and surgery-related vomiting. They, too, have shown the superior efficacy, safety, and cost-effectiveness of ondansetron over other classes of antiemetics, (such as dopamine receptor antagonists, antihistamines, and anticholinergics) (66,67). However, some aspects of antiemetic therapy are still controversial: (a) the risk factors for postoperative vomiting in surgical patients; (b) the incidence of postoperative vomiting when such risk factors aggregate; (c) the place for or against prophylaxis in high

risk patients; and (d) the pharmacological cocktail to be employed in such high risk patients in order to optimize the response to therapy.

The recent systematic reviews on this subject (31,66) identify the following risk factors as contributors to postoperative nausea and vomiting:

1. Females in childbearing age group.
2. Previous history of nausea and vomiting.
3. Non-smoking patients.
4. Type and location of surgery.
5. Type of anesthesia.
6. Duration of anesthesia.
7. Perioperative use of opioids for pain control.

New Indications

Ondansetron has been used for certain other conditions, where first-line treatment has failed or produced unsatisfactory results. For example, ondansetron was effective as an antidiarrheal agent in carcinoid syndrome (70). Opiate-induced postoperative pruritus has also been successfully treated with ondansetron (10,36). Recently, 5-HT₃ antagonism was found to be effective in controlling postoperative shivering in normothermic patients (9). In view of the current advances in basic science research that explores the widespread physiological and pathological effects of 5-HT, the list of such unconventional uses of ondansetron is likely to expand in the future.

Gastrointestinal motility disorders

Irritable bowel syndrome (IBS): 5-HT₃ (alosetron, granisetron, and ondansetron) and 5-HT₄ (SB-207266A) antagonists reduce visceral sensitivity and have inhibitory effects on motor activity in the distal intestine. Early clinical studies suggest that these agents may have a role in painful, diarrhea-predominant IBS. In a double-blind, placebo-controlled cross-over study of fifty patients with IBS, ondansetron (16 mg, 3 times daily for 4 weeks) reduced bowel frequency ($P = 0.035$) and improved stool consistency ($P = 0.002$). No statistically significant improvement was seen in abdominal pain or distension. Ondansetron also significantly improved the upper gastrointestinal symptoms of post-prandial epigastric discomfort ($P = 0.008$), flatulence ($P = 0.022$) and heartburn ($P = 0.003$) (41).

Ondansetron may affect gut sensitivity and pain in patients with IBS. In addition to causing significantly firmer stools in six IBS patients and ten healthy volunteers ($P < 0.01$), ondansetron (16 mg, 3 times/day) also increased the rectal sensory threshold to electrical stimulation in the six IBS patients and decreased their maximum tolerated volumes to distension. Furthermore, patients with IBS experienced significantly fewer daily episodes of pain while on ondansetron (23).

Pruritus

Ondansetron has been shown to have significant effect on pruritus induced by morphine or alfentanil. However, ondansetron has no effect on the pruritus in hemodialysis patients. This discrepancy suggests that the antagonistic properties of ondansetron regarding the 5-HT₃ receptor may underlie ondansetron's clinical effects on pruritus.

Several examples follow, which show ondansetron's relationship to pruritus relief. At 8 mg i.v., ondansetron significantly decreased spinal or epidural morphine-induced pru-

ritus in a prospective, randomized, double-blind, placebo-controlled study conducted on 100 patients. The ondansetron group showed a success rate of 70 vs. 30% for the placebo group ($P < 0.05$) (10). In a study on 60 consecutive non-breastfeeding women, ondansetron (0.1 mg/kg i.v.) significantly reduced the incidence of intrathecal morphine-induced pruritus (25%) as compared with a placebo group (85%) and a group receiving diphenhydramine (80%) (both $P < 0.05$) (74). In a randomized, placebo-controlled, double-blind, cross-over study, orally administered ondansetron had a small, but significant positive effect on pruritus associated with chronic liver disease (45).

In a prospective, randomized, double-blind, placebo-controlled study conducted on 80 patients, ondansetron (4 mg i.v. at 30 min before alfentanil 10 mg/kg i.v.) significantly reduced the incidence of scratching (42.5 vs. 70% in the placebo group, $P = 0.013$). The incidence of itching in the ondansetron group was less than that in the placebo group but the difference was not statistically significant (30 vs. 42.5%, respectively, $P = 0.245$) (36).

Ondansetron produced apparent subjective ameliorations of pruritus in cholestatic patients (30). In addition, ondansetron has been shown to be effective in treating renal itch (46). However, as mentioned earlier, ondansetron (8 mg, 3 times daily for two weeks) did not improve pruritus in hemodialysis patients, as demonstrated in a prospective, placebo-controlled, double-blind crossover randomized study involving 16 hemodialysis patients with persistent pruritus (5).

Alcoholism

Ondansetron appears to be a promising agent for the treatment of alcoholism. Extensive and growing literature indicates that 5-HT₃ receptors are involved in several important neurochemical and behavioral effects of alcohol, including alcohol intoxication, as well as alcohol seeking behavior and addiction. There is strong evidence that alcohols, including ethanol, alter the function of the 5-HT₃ receptor, possibly through actions on the receptor protein itself (37). Neurophysiological studies have demonstrated that 5-HT₃ receptor antagonists block ethanol potentiation of 5-HT₃ receptor-mediated ion currents (37).

Evidence from behavioral pharmacological studies suggests that the 5-HT₃ receptor is likely to be involved in alcohol's rewarding effect (6). For example, 5-HT₃-receptor antagonists decrease alcohol consumption in most animal models and across different species (6,42). In addition, reduced mesolimbic dopamine and 5-HT functions have been observed during alcohol withdrawal in common stock rats (42).

A role for ondansetron in the treatment of alcoholism is supported by human studies, although the results of some studies are controversial. Two studies suggested that ondansetron is useful in the treatment of alcoholism. The studies concluded that ondansetron attenuated low-dose alcohol-induced positive subjective effects, including the desire to drink (28). In a double-blind, randomized, placebo-controlled clinical trial involving a total of 321 patients with diagnosed alcoholism, ondansetron decreased drinking and alcohol preference, and increased the abstinence rate among early onset alcoholics, who respond poorly to psychosocial treatment alone (27,29).

A third group reported a mixture of both stimulant and sedative interactions between ondansetron and alcohol. These studies contrast with that of Doty and co-workers, who found no effect of ondansetron on alcohol-induced mood (21). The reasons for the controversial results are unclear. Possible explanations include a difference in the route of on-

dansetron administration, and a difference in the experimental settings (group vs. individual). Rigorous double-blind clinical studies are necessary to resolve this discrepancy.

Cocaine sensitization and tolerance

5-HT₃ receptor stimulation during continuous and intermittent cocaine administration is an important link in the development of behavioral tolerance and sensitization (33). Ondansetron produced long-term blockade of the expression of cocaine sensitization as evidenced by the observation that a daily subcutaneous injection of 1.0 mg/kg ondansetron blocked the expression of sensitization in rats pretreated for 14 days by daily subcutaneous injections of 40 mg/kg cocaine (32).

Opioid withdrawal syndrome

Administration of ondansetron (1, 2, and 4 mg/kg i.p.) to rats receiving naloxone after chronic morphine decreased the intensity of withdrawal signs such as increased defecation, jumping and wet-dog shakes, as well as elevated the nociceptive threshold values which were decreased by precipitated withdrawal. These effects of ondansetron may be explained by interference with serotonergic mechanisms involved in the regulation of these withdrawal symptoms. It was, therefore, suggested that ondansetron could be useful in the treatment of opioid withdrawal symptoms in heroin addicts (50).

Psychosis

Psychosis is a condition associated with raised mesolimbic dopamine activity. Accumulating evidence from animal and human studies indicates that ondansetron may affect neurotransmission within mesolimbic brain regions. Thus, ondansetron may be beneficial to patients with psychosis. In an open-label study involving 20 schizophrenic patients with neuroleptic-induced tardive dyskinesia, ondansetron (12 mg/day for 12 weeks) produced a statistically significant improvement in tardive dyskinesia and psychotic symptoms (61). In another study ondansetron attenuated visual hallucinations, delusional ideation and confusion, and was well tolerated (44).

Anxiety

Animal studies. Ondansetron effects on anxiety are controversial. At 0.3 to 3.0 mg/kg, i.p. ondansetron has been shown to have anxiolytic effect in rats in a modified open-field test (8,54). In a novel animal model of anxiety, which measures approach-conflict behavior, ondansetron, at 0.01, 0.1, and 1 mg/kg i.p., had significant anxiolytic effect (as compared to naive mice), but was less potent than diazepam, 1 mg/kg (58). In pigeons, ondansetron, 100 mg/kg, i.v., had a modest effect of releasing behavior suppressed by punishment (anxiolytic-like action), which was highly dependent on the intensity of punishment applied (16). Ondansetron, 0.1 mg/kg, i.p., had no effect, however, in rat pup ultrasonic vocalization (USV) model, a putative animal model reflecting anxiety. In contrast, the selective 5-HT_{2A} receptor antagonist, MDL 100,907 (0.1 mg/kg, i.p.) completely prevented the paroxetine-induced reduction of UCV (60).

Human studies. Studies in humans led also to controversial results regarding the anxiolytic effect of ondansetron. In a study on 12 healthy volunteers, ondansetron (0.15 mg/kg) significantly reduced behavioral, physiological and neuroendocrine responses to μ -chlorophenylpiperazine, an anxiety-inducing drug (13). However, ondansetron (0.24

mg/kg) had no effect in reducing anxiety in patients with generalized anxiety disorder (40). Nor did it significantly affect the severity of withdrawal symptoms or the levels of anxiety experienced during the discontinuation of benzodiazepines by long-term users. This was shown in a randomized double-blind human study in 97 patients, each of whom received 2mg ondansetron twice daily (57). In a human study on 14 patients with panic disorder and social phobia, ondansetron did not alter pentagastrin-induced cortisol increase, although it significantly prolonged pentagastrin-induced increase in the levels of adrenocorticotrophic hormone (43).

Tourette's syndrome

An open-label pilot study evaluated the effect of ondansetron in Tourette's syndrome. Six men with Tourette's syndrome (14 to 48 years old), who were resistant to haloperidol, participated in the study. Assessments included the Yale Global Tic Severity Scale (YGTSS), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), and Tourette's syndrome-Clinical Global Impression (TS-CGI) scale. The maximal ondansetron dosage (8–16 mg per day) was given for 3 weeks. Ondansetron treatment was associated with a significant decrease in the severity of tics. Two patients showed a definite response (score improvement of 40% or more), and two showed a probable response (>25%). Two patients did not improve. Side effects were transient and included abdominal pain ($n = 5$) and constipation ($n = 2$). Thus, ondansetron may have anti-tic effects in some Tourette's syndrome patients (65).

RECENT PRECLINICAL STUDIES

Effects of Ondansetron on Ion Channels

5-HT₃, GABA_A, glycine, and nicotinic acetylcholine (nACh) receptors all belong to a superfamily of ligand-gated ion channels. The subunits of these receptors exhibit extensive amino acid sequence homology (7). Because of these similarities, many drugs that act on one type of receptor often act on other receptors in this group as well. For example, some 5-HT₃-receptor antagonists act on the GABA_A receptor complex (GABA_AR) in addition to 5-HT₃ receptors (34).

The primary author of this review and his colleagues have demonstrated the local analgesic property of ondansetron by showing that ondansetron blocks sodium channels in rat brain neurons (72). The same team also demonstrated an increase in pain threshold in rat tail-flick test by subcutaneously injected ondansetron (72). These observations may have clinical implications, because they suggest that intraoperative administration of ondansetron as prophylaxis for postoperative emesis might also lead to a potentiation of the analgesic effect of opioids administered for postoperative pain control. This possibility needs to be verified by clinical studies.

The same team also showed that ondansetron competitively suppresses the chloride currents activated by GABA or glycine in patch-clamped hypothalamic and hippocampal neurons of rats (71,73). By preventing the influx of Cl⁻, subsequent hyperpolarization was also inhibited. Furthermore, ondansetron competitively inhibited glycine-induced depolarization in neonatal neurons and glycine-induced hyperpolarization in mature neurons of

rats (73). The authors suggested that this anti-glycine property of ondansetron may play a significant role in the ondansetron-induced seizures observed in vivo.

TOXICOLOGY

The side effects of ondansetron should be reviewed in the context of its clinical use. Ondansetron is currently used to prevent and treat nausea and vomiting associated with chemotherapy, radiation treatment and general anesthesia. In the evaluation of the side effects of ondansetron its risk-benefit profile should be considered. As discussed previously, nausea, whether associated with chemotherapy, radiotherapy or anesthesia, significantly affects quality of life and vomiting causes substantial pathophysiological aberrations.

The toxic effects of ondansetron can be related to its pharmacodynamic and pharmacokinetic properties. Ondansetron acts by blocking serotonergic transmission at the 5-HT₃ receptors located peripherally on vagal afferents in the gastrointestinal system and centrally in the chemoreceptor trigger zone and the vomiting center of the central nervous system. The specificity of ondansetron for 5HT₃ receptors is not absolute, and it may act on other, currently identifiable, serotonin receptors, such as 5-HT₁, 5-HT₂, and 5-HT₄ receptors (68). Ondansetron exhibits also some interactions with other classes of receptors including μ -opioid, α -adrenergic, GABA, and glycine receptors (20,71,73).

The pharmacokinetic properties of ondansetron include its wide volume of distribution, high plasma protein binding, extensive hepatic cytochrome P-450 enzymatic metabolism and rapid renal clearance. Certain disease states that affect the volume of distribution and interactions with drugs that interfere with plasma protein binding, metabolism and clearance of ondansetron can exacerbate its toxic effects. It is of interest that in elderly and female patients with a decreased clearance of ondansetron no dosage adjustment has been recommended when ondansetron is used for the prevention or treatment of postoperative nausea and vomiting. Regarding concern about overdose, ondansetron has a high therapeutic index, and accidental ingestion of ten times the recommended daily dose with no fatality has been reported (75). Accidental overdose has no specific antidote and supportive treatment with adequate hydration is recommended.

Several side effects are linked to ondansetron. Its most commonly reported side effect is headache (59). Though the exact mechanism of ondansetron-induced headache is not known, a weak antagonistic effect at 5-HT₁ receptors may precipitate headache in susceptible individuals, including migraine sufferers and postoperative patients who are exposed to caffeine withdrawal due to fasting requirements for general anesthesia. By rapid intravenous administration ondansetron can produce significant hypotension with tachycardia that can lead to syncopal episodes in awake patients. In rare situations, ondansetron can induce angina with electrocardiographic evidence of myocardial ischemia (11). 5-HT receptor subtypes are widely distributed in the coronary arteries and their involvement in this phenomenon is conceivable.

Abnormal bowel function (constipation more often than diarrhea), seizure activity and excessive fatigue and weakness have also been associated with ondansetron (59). 5-HT has some role in the normal neural and hormonal control of bowel activity, and pharmacological blockade of widely distributed 5-HT₃ receptors in the intestinal tract can lead to

abnormal bowel function. It is known that diarrhea is a pertinent symptom of carcinoid tumors that secrete excessive amounts of 5-HT (55).

Ondansetron has been shown to inhibit GABA and glycine receptor activity in animal models; extrapolation of these findings to humans may explain the reported incidents of grand mal seizures in clinical practice. The excessive weakness felt by patients that are placed on long-term antiemetic prophylaxis might be explained by ondansetron's ability to bind to the amino acids of the nicotinic receptors at the neuromuscular junction and to produce neuromuscular blockade (51). This property has not been, however, fully evaluated. Other reported side effects, such as malaise, fever and abnormal liver function (transient elevations in aspartate transaminase and alanine transaminase levels), are difficult to attribute to ondansetron. In oncology patients these side effects can also be precipitated by underlying malignancy, concomitant chemotherapy or radiation treatment. In postoperative patients they can also be induced by stress due to surgery and/or anesthesia (59).

Ondansetron has been studied in special patient populations. For example, in the pediatric population above the age of two, the adverse effects of ondansetron at recommended doses are not only weaker but also better tolerated by children (75). Experience in children under two years of age is limited.

Animal studies show no embryocidal or teratogenic effects of ondansetron. No such effects were reported in humans. In animals ondansetron is excreted in breast milk and, in keeping with the pattern of many other drugs, the same should be expected in humans. Of importance to another patient group, the oral formulation of ondansetron contains phenylalanine; hence, it should not be administered to phenylketonurics. There are no clinical studies to establish its safety in patients with significant hepatic or renal impairment.

The side effect profile of ondansetron should be considered along with its efficacy in preventing unwanted nausea and vomiting in cancer patients exposed to chemotherapy or radiation treatment and in surgical patients to whom general anesthesia has been administered. Alternatives, such as dopaminergic receptor blocking drugs, antihistamines and anticholinergics, are available, but at the expense of unwanted side effects, including excessive sedation and extrapyramidal symptoms. The long-term cost of treating nausea and vomiting in these patient populations should also be critically analyzed (4). Finally, the quality of life issues deserve appropriate attention and consideration.

SUMMARY AND FUTURE DIRECTIONS

Ondansetron was introduced into clinical practice in the 1980s and was widely accepted and used in the 1990s as the antiemetic of choice for the prevention and treatment of nausea and vomiting in cancer treatment and as a sequel to anesthesia and surgery. In this decade, it could be considered as the gold standard, against which any future antiemetic would be judged. Ondansetron reached this enviable position because of the vast knowledge on 5-HT generated by basic science research and the subsequent clinical development that demonstrated the superior efficacy, safety and pharmacoeconomic profile of ondansetron. However, this is not the end of the road for ondansetron and other 5-HT₃ antagonists. Further challenges, such as the management of anticipatory and delayed vom-

iting in cancer treatment and the need for a “rescue” antiemetic in surgical patients, do exist. Hence, the investigative work should continue with new directions in research to address these issues and to explore other non-conventional uses of ondansetron in clinical practice.

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