Department of Pharmacology
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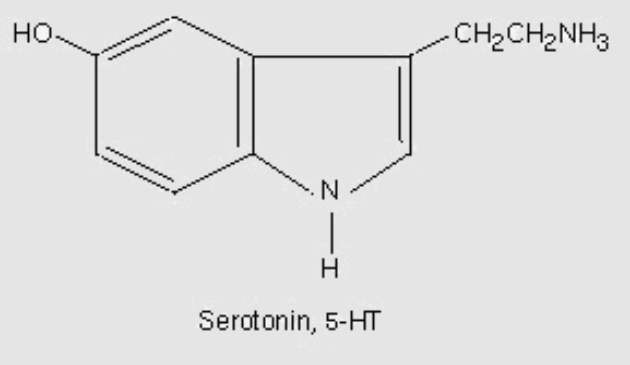
King Saud University

Serotonin receptors antagonists as antiemetics



Serotonin, 5-HT

Done By:
Meshael Bin Mowanie
Dimath AlYemni
Sarah AlGhamdi
Lina Ba'abbad

Supervised By:
Dr. Hanan Hagar

From our hearts to yours,
We dedicate this research to everyone who has helped us through long hard times.
We also would like to thank our amazing friends and families who gave us support and comfort to bring out our best results. Sarah, Lina, Dimath, Meshael.
'There are high spots in all our lives and most of them come out through encouragement from someone else'

Source: unknown

I. SUMMARY

In the mide-1980s it was discovered that serotonin (5 hydroxytryptamine, 5-HT) was at least partially responsible for producing chemotheraphy-induced and vomiting. It was there for realized that serotonin receptor blockade with antagonists could inhibit chemo-therapy induced nausea and vomiting. However, faced with the ever- growing availability of new 5-HT3 compounds, there is a need to understand if there are real difference in efficacy and safety among these compound.

5-HT3 antagonists have different chemical structures and receptor binding affinity. Granisetron dolasetron and its major metabolite are pure 5-HT3 antagonists. While ondansetron and tropisetron are weak antagonists at the5-HT4 receptor, ondansetron has also been demonstrated to bind at other serotonin receptors and to the opioid μ receptor.

The half-lives of granisetron, tropisetron and the active metabolite of dolasetrom are 2 to 3 times longer than that of ondansetron. These observations initially suggested that more frequent ondansetron administration would be required. However, it has now been shown that receptor blockade dose not correlate with elimination half-life and all 5-HT3 antagonists can be effectively administered once daily.

Comparative clinical trials using various doses, route and regiments of administration have been conducted with 5-HT3 antagonists. Despite some trail design shortcomings most of the studies show equal efficacy between the agents, especially in moderately emetogenic chemotherapy and mild, infrequently occurring adverse effects.

The efficacy of 5-HT3 antagoniss in controlling delayed nausea and vomiting from chemotherapy is less well studied. Further, there is no good scientific rationale for the use of 5-HT3 antagenists in controlling delayed nausea and vomiting since serotonin has not been shown to released during the delayed phase

Because the 5- HT3 antagonists perform similarly in the clinical setting, pharmacological differences do not seem to translate into therapeutic difference. There is also no appreciable difference in the incidence or severity of adverse effects among the 5-HT3 antagonists; Determination of clinical use may then be driven by cost.

II. NAUSEA AND VOMITING

1. Definition:

Nausea:

Unpleasant sensation associated with awareness of the urge to vomit, its usually felt in the back of the throat and epigastrium, and is accompanied by loss of gastric tone, duodenal contractions and reflex of intestinal contents into the stomach.

Vomiting or Emesis:

Is the forceful expulsion of gastric contents from the mouth and is brought about by the powerful sustained contraction of abdominal muscles, decent then diaphragm, and opening of gastric cardia.

(Watcha and White, 1992)

(Morrow et al. 1995).

2. Pathophysiology:

Vomiting results from an intricate series of physiological events mediated by humoral factors and afferent fibe and both inhibition and excitation of somatic visceral musculature that are ultimately coordinated by vomiting center.

The emetic center is a nucleus of cells located in the medulla and is the motor center responsible for the coordination of emesis. Afferent input to the emetic center originates from at least four (4) sources:

1. chemoreceptor trigger zone (CTZ)
2. the cortex
3. the vestibular apparatus
4. gastrointestinal tract.

Vomiting occurs when afferent impulses are send from the emetic center to the salivation center, abdominal muscles, respiratory center and cranial nerves.
(Gregory and Ettinger, 1998)

Parvicellular reticular formation has access to the motor pathway responsible for the visceral and somatic output involved in vomiting. This area is situated in the lateral reticular formation close to the tractus solitarius in the brain stem and is thought to be the emetic center.
(Watcha and White, 1992), (Morrow et al., 1995).

Stimuli from several areas within the central nervous system can affect the emetic center (fig. 1), these include afferent from the pharynx, gastrointestinal tract and mediastinum, as well as afferent from the higher cortical center (including the visual center and the vestibular portion of the eight cranial nerve) and the chemoreceptor trigger zone (CTZ) in the area postrema. (Watcha and White, 1992). The gastrointestinal tract is directly connected to the emetic center via nucleus tractus solitarius and its also contains afferent fibers which terminate at the CTZ. Because of its location within the area postrema , the CTZ is exposed to both cerebrospinal fluid and the systemic circulation thus; substances circulating in both fluids can stimulate CTZ to release neurotransmitters. All of afferent inputs received by the vomiting center are controlled by neurotransmitters and their receptors. (Gregory and Ettinger, 1998), (Scarahtiro et al., 1992).

The area postrema of the brain stem is rich in dopamine, opioid and serotonin receptors. The nucleus tractus solitaraius is rich in enkephains and histaminic and muscarinic cholenergic receptors. These receptors may play an important role in the transmission of impulses to the emetic center. (Watcha and White, 1992). Dopamine, histamine, acetylcholine and sertonin are all neurotransmitters which involved in the emetogenic pathways stimulated by radiation and chemotherapy.

Figure 1.

Anatomic structures involved in the vomiting reflex. Sites of action of common antiemetic drugs are labeled as follows: 1. site of action of sedative; 2. site of action of antihistamines and anticholinergics; 3. site of action of dopamine antagonists; and 4. proposed sites of action serotonin antagonists. The vomiting reflex is mediated through the vomiting center. This center receives impulses from afferent fibers from the stomach and intestines and from fibers in the chemoreceptor trigger zone. It sends out impulses via afferent fibers to the muscles of the throat, epiglottis, and stomach.

Receptors for each of these neurotransmitters are found in abundance in the emetic center, the CTZ and the gastrointestinal tract. Activation of these receptors by chemotherapy, metabolites and/or neurotransmitter release caused by chemotherapy all may be responsible for inducing nausea and vomiting.
(Fig. 2)

Serotonin found in high concentrations within the enterochromaffin cells in the gut $5HT_3$ receptors are widely distributed in peripheral tissues, the nucleus tractus solitarius and the CTZ where most vagal afferents enter the brain. Peripherally, chemotherapy and radiation cause release of serotonin from enterchromaffin cells which activate the abdominal vaga afferent. (Gregory and Ettinger, 1998).

3. Causes of vomiting:

1. Cancer chemotherapy
2. During pregnancy
3. Postoperative vomiting
4. Gastroenteritis
5. Motion sickness

and other causes are listed in table1.

Table 1.Causes of Vomiting

1. Ingestion of certain substances present in food and the environment. 2. Ingestion of certain drugs, particularly opiates, general anesthetics, and antineoplastic drugs 3. Motion or other effects on the vestibular apparatus. 4. Infection (part of the prodrome of many infections) 5. Respiratory problems such as violent coughing 6. Cardiovascular disease such infarction 7. Disorders of the gastrointestinal tract: a. Gastrointestinal tract obstruction b. Mucosal lesions such as ulcers, inflammation, and atrophy c. Liver disease d. Pancreatic and small intestinal diseases e. Diseases of the components of the gut wall (collagen, smooth muscle, nerve) f. Peritonitis	1. Renal diseases such as renal failure, pyelonephritis, uremia, and uremic colic 2. Metabolic and endocrine disorders and conditions such as diabetic ketoacidosis, hyperparathyroidism, adrenal insufficiency, and pregnancy 3. Gynecologic disorders such as pelvic inflammation and complications or pregnancy 4. Normal pregnancy 5. Neurologic disorders such as increased cranial pressure, hemorrhage, epilepsy, meningitis, migraine, vertigo, Meniere's syndrome, and brain metastases 6. Psychiatric disorders including bulimia, rumination, and anorexia nervosa 7. Drug withdrawal syndromes 8. Radiation Therapy

5. Clinical presentation and diagnosis:

Signs and symptoms:

The signs and symptoms of vomiting - induced metabolic disturbances include the following:

- Dehydration, suggested by oliguria, weight loss, mental confussion and reduced tissue turgor.
- Sodium depletion, suggested by thirst and hypotension.
- Potassium depletion, suggested by muscle weakness or cardia rhythm disturbances.
- Alkalosis, which can result from loss of hydrogen ions in the vomitus, and the concentration of extra cellular fluid secondary to fluid loss.

Diagnosis

An accurate diagnosis is essential before treatment begins because symptomatic therapy may be contraindicated (e.g. GI obstruction, acute appendiatis or cerebral edema) or assessment of underlying disease could be complicated by the sedative properties of most antiemetic therapy.

The appearance, frequency and timing of vomiting together with associated specific and nonspecific symptoms such as jaundice, dehydration, diarrhea etc. are important in making diagnosis.

5. Theraputic Plan:

- Treat cause if it can be identified
- Assess for fluid and electrolyte loss
- Give appropriate symptomatic drug treatment after considering contra indications and adverse drug actions.
- For unexplained vomiting, continue with diagnostic examination.

6. Treatment:

Pharmacotherapy by Antiemetics.

III. ANTIEMETIC DRUGS

Four Major neurotransmitter systems appear to play important roles in mediating the emetic response:-

- Dopamenergic system
- Histaminergic system
- Cholinergic system
- (5-HT_3). Serotonergic System

As there are four different types of receptors, there are at least four sites of action of the antiemetic drugs. Antiemetic agents may have actions at more than one receptor, but they tend to have a more prominent action at one or two receptors. Hence, a combination of drugs will probably have greater antiemetic action than a single drug.

There are different anti-emetic agents used for different conditions. And they are classified as: -

1 - Phenothiazines.
2 - Butyrophenones.
3 - Antihistaminics.
4 - Anticholinergics.
5 - Benzamides.
6 - Sertonin Antagonists.
7 - Tricyclic antidepresents.
8 - Other drugs as ephedrine.

Table 2. Receptor Site Affinity of Antiemetic Drugs (modified from peroutka *et al*. and Hamik *et al*.)

Pharmacologic Group (drug)	Dopamin(D_2)	Muscarinic Cholinergic	Histamine	Serotonin
1. Phenothiazines				
Fluphenazine	++++	+	++	-
Chlopromazine	++++	++	++++	+
Prochlorperazine	++++			
2. Butyrophenones				
Droperidol	++++	-	+	+
Haloperidol	++++	-	+	-
Demoperidone	++++			
3. Antihistaminics				
Diphenhydramine	+	++	++++	-
Promethazine	++	++	++++	-
4. Anticholinergic: Scopolamine	+	++++	+	-
Benzamides: Metoclopramide	+++	-	+	++
5. Antiserotonin				
Ondansetron	-	-	-	++++
BRL 43694 (Granisetron)	-	-	-	++++
Zacopride	-	-	-	++++
RG 12915	-	-	-	++++
6. Tricyclic antidepressants				
Amitriptyline	+++	+++	++++	-
Notriptyline	+++	++	+++	-

The number of positive (+) signs indicates degree of activity at receptor. The negative (-) sign indicates no activity.

1. Phenothiazine:

The antiemetic actions of Phenothiazines have been attributed to their ability to block receptors in the CT2, specifically the dopamenergic receptors.

- Chlorpromazine and Promethazine have been used for years in prevention and treatment of postoperative emesis, particularly if apoid have been administered,
- Prochlorperazine and Perphenazine are effective therapeutic agents in the management of postoperative emesis when morphine or mepridine have been administered, they have shorter durations of action than the commonly used apoid analgesis, and repeated dosing may be required.
- Dixyrazine, is a Phenothiazine with less sedative action, has been used successfully as an antiemetic in children undergoing strabismus surgery.

2. Butyrophenones:

The neuroleptic drugs, Haloperidol and Droperidol, are major tranquilizing drugs that posses significant antiemetic activity as a result of their antagonistic properties at the dopamine receptor.

Haloperidol and Droperidol are used in management of postoperative nausea and vomiting.

- Higher doses of Droperidol (2.5-5 mg adults or 50 – 75$\mu g.kg^{-1}$ in children) are associated with significant drowsiness and can delay discharge.

- Routine use of Droperidol is not recommended for patients undergoing out patient surgery, as it has extrapyramidal side effects and cause restlessness and anxiety following discharge.

- Lower does of Droperidol (10-20 μg.kg^{-1}) have been successfully in procedures associated with a moderately high incidence of emesis (e.g. laparascopy) but have limited efficacy for the more emetic procedures (e.g. strabismus).

- Droperidol (50-75μg.kg^{-1}) is partially effective prophylactic antiemetic.

* Domperidone, a benzimidazole that is structurally similar to Droperidol, was alleged to be an effective antiemetic with fewer central nervous system side effects than Droperidol.

- It acts by increasing the motility of the upper gastrointestinal tract and it has a blocking effect on the CTZ.

- Used in the treatment of postoperative emesis when administered in the recovery room.

3. Antihistaminics:

- Dimenhydrinate, hydroxyzine, cyclizine are Antihistaminics, that act on the vomiting center and the vestibular pathways.
- These compounds are particularly useful in the prophylaxis and therapy of motion sickness and in the control of emesis following middle ear surgery.

4. Anticholinergics:

It has been suggested that different Cholinergic receptor sites are present in the cerebral cortex and pons and that compounds with specific activity at these receptors could from the basis for effective antiemetic drugs.

- The addition of Anticholinergic drugs such as atropine or scopolamine (hyoscine) to an apoid compound for premedication olecreases emesis.
- Transdermal scopolamine is effective in controlling motion sickness and significantly decreases the incidence of server nausea and vomiting after outpatient laparascopy and after epidural morphine administration.
- They can produce undesirable side effects such as:-

  - Dry mouth.
  - Sedation.
  - Visual disturbances.
  - Memory dysfunction.
  - Dysphoria.
  - Confusion.
  - Disorientation.
  - Hallucinations.

5. Benzamides:

Metoclopramide is a benzamide with both central and peripheral antiemetic action. In addition to its ability to block dopamenergic receptors at the CTZ, Metoclopramide increases lower esophageal sphincter tone and enhances gastric and small bowel motility. Thereby preventing the delayed gastric emptying produced by the opoid analgesics, although it is not effective in controlling motion sickness associated with linear or angular acceleration, Metoclopramide also has some peripheral Cholinergic action,

High doses of Metoclopramide (1-2 $mg.kg^{-1}$) are effective in managing chemotherapy – included emesis.

More conventional antiemetic dosage (0.1 – 0.2 kg^{-1}) have been used in the prophylaxis and treatment of postoperative emesis in adults and children because these doses are not associated with significant sedative activity.
Metoclopramide appears to be an effective antiemetic in patient receiving opiod analogies as preanesthetic medication, during surgery in the immediate postoperative period.

Metoclopramide has a short half-life and should be administered immediately before or just after the end of surgery to have a reliable antiemetic effect in the early postoperative period,

When Metoclopramide is used in the large doses required to prevent emesis during end after chemotherapy, is associated with a high incidence of dystonic reaction, particularly in children even in the usual perioperative dose of 0.1-0.2 $mg.kg^{-1}$, children are more prone to develop extrapyramidal side effects from Metoclopramide than are adults.

Methobenamide has less antiemetic action than metodopramide but can be administered regularly in children.

Eisapride is a benzamide with a strong prokinetic effect on the gastrointestinal system secondary to acetylcholine release a the myenteric plexus, This Cholinergic action results in increased lower esophogical pressure and motility in the entire gastrointestinal tract including the large bowel. It has greater ability than Metoclopramide to reverse morphine-included gastric stasis and is not associated with extrapyramidal side effects, since it has no activity at the central dopaminergic receptors, However, cisapride does not block the decrease in lower esophageal tone following the antagonism of neuromuscular blockade by neostigmine, and hence its role in anesthesia remain unclear.

Alizapride is an investigational substituted benzamide with a greater potency than Metoclopramide and fewer side effects, it does not appear to be as effective as high-dose Metoclopramide.

Clebopride is a benzamide with more potent antiemetic activity than metodopride, it increase, gastrointestinal peristalsis, and at doses that do not result in extrapyramidal symptoms or hyperprolactinemia, it has a mild tranquilizing effects.

Levosulpride is another investigational benzamide compound with antiemetic action, but it is less potent than Metoclopramide.

6. Ephedrine:

an indirectly acting sympathomimetic drug can prevent motion sickness.

- It is also effective In emesis that occurs secondary to the hypertension associated with spinal anesthesia.

(Biebuyck JF , 1992).

IV. The 5-HT receptors and their function

The 5-HT receptors:

Serotonin receptors are a large and diverse family consisting of 13 GPCRs plus 1 ligand-gated ion channel (5-HT_3). Serotonin receptors are classified into 7 groups according to their ligand-binding affinity profiles, molecular structures, and intracellular transduction mechanisms.(Figure 3)

Figure 3. Phylogenetic trees for human dopamine (D) and serotonin (5-HT) G protein–coupled receptors. A, Phenogram representing genetic distances. This analysis supports the suggestion that dopamine, 5-HT_1, 5-HT_5, 5-HT_7, and 5-HT_4 receptors evolved from a common ancestor after the initial divergence of the 5-HT_2 and 5-HT_6 receptor subtypes.[1] B, Most parsimonious tree. The 3 major divisions in the evolutionary topology correspond to a signal transduction mechanism rather than ligand specificity: coupling to G_q proteins (leading to increased phosphoinositol), G_s proteins (increased cyclic adenosine monophosphate [cAMP]) and G_i proteins (decreased cAMP). The 5-HT_{5A}–signalling mechanism remains unclear, and this is convergent with its position in the evolutionary topology based on sequence. PI indicates phosphoinositol; AC, cAMP; ↑, increase; and ↓, decrease.

The 5-HT_1 receptor family:

The human 5-HT_1 receptor subfamily includes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} receptors; their activation leads to inhibition of cAMP synthesis through coupling to $G_{i/o}$ proteins.

5-HT_{1A}

This receptor subtype is widely distributed in the CNS, particularly the hippocampus, septum and amygdala, areas. It is thought to be associated with the control of mood. 5-HT_{1A} receptors seem to modulate anxiety: mice lacking the 5-HT_{1A} receptor show increased anxiety responses in behavioral tests (Ramboz et al,1998) (Parks et al,1998). The receptor is negatively coupled to adenylyl cyclase, and principally causes hyperpolarisation. Agonists facilitate male sexual behavior in rats, hypotension, increase food intake, produce hypothermia, and act as anxiolytics. This receptor has also been widely implicated in depression. Example of agonists are buspirone

5-HT_{1B}

The 5-HT_{1B} receptors are concentrated in the basal ganglia, striatum and frontal cortex. These may act as autoreceptors and are negatively coupled to adenylyl cyclase. 5-HT_{1B} receptors function as autoreceptors on serotoninergic terminals and as heteroreceptors controlling the release of other neurotransmitters. 5-HT_{1B} receptor–deficient mice show enhanced aggressive behavior, elevated alcohol consumption, and shorter latency for cocaine self-administration (Crabbe et al,1996). Agonists inhibit aggressive behavior and food intake in rodents. These receptors, which have been identified only in rodents and are apparently absent in humans, are thus only of theoretical interest at present. These receptors may be the counterpart of the 5-HT_{1D} receptor found in other species.

Interest in 5-HT_{1B} receptor agonists has been generated by the antimigraine properties of sumatriptan, a non selective 5-HT_{1D} and 5-HT_{1B} receptor agonist with low selectivity against other receptors in functional studies.

5-HT_{1D}

The 5-HT_{1D} receptors (formerly termed $5HT_{1Da}$) has 63% overall structural homology with the 5-HT_{1B} receptors (formerly 5-HT_{1Db}). They are Located primarily in the CNS, Low levels of the 5-HT_{1D} receptor mRNA are found in the rat brain, predominantly in the caudate putamen, nucleus accumbens, hippocampus and cortex, but also in the dorsal raphe and locus coeruleus. these receptors may play a role as a presynaptic heteroreceptor or as a terminal autoreceptor, being thus involved in the inhibition of neurotransmitter release by mediating a negative feedback effect on transmitter release. This subtype is also found in vascular smooth muscle mediating contraction. The receptor is negatively linked to adenylyl cyclase (Weinshank et al, 1992). The location of 5-HT_{1D} receptor mRNA in the raphe, suggests that it may function as an 5-HT autoreceptor. This data could be further substantiated by the use of ketanserin and ritanserin, which in addition to their high affinity for the 5-HT_{2A} site also have high affinity for the 5-HT_{1D}, but not the $5HT_{1B}$ site. agonists at this site are effective in treating acute migraine headaches.

5-HT_{1E}

The 5-HT_{1E} receptor is concentrated in the caudate putamen with lower levels in the amygdala, frontal cortex and globus pallidus. It is negatively linked to adenylyl cyclase. There are no reported selective or high affinity ligands for this receptor (except for 5HT itself) and its function is currently unknown (Stephen and Peroutka, 1993).

5-HT_{1F}

This receptor subtype is most closely related to the 5-HT_{1E} receptor. mRNA coding for the receptor is concentrated in the dorsal raphe, hippocampus and cortex of the rat and also in the striatum, thalamus and hypothalamus of the mouse. 5-HT_{1F} receptor mRNA has been detected in human brain and is also present in the mesentery and uterus. The

receptor is negatively linked to adenylyl cyclase. The antimigraine 5-$HT_{1B/1D}$ agonist, sumatriptan, has almost equal affinity for the $5HT_{1F}$ as the 5-$HT_{1B/1D}$ receptors. Thus, it has been hypothesised that the 5-HT_{1F} receptor might be be a target for drugs with antimigraine properties. 5-HT_{1F} mRNA has been detected in the trigeminal ganglia, whose stimulation leads to plasma extravasation in the dura, a component of neurogenic inflammation which is thought to be a possible cause of migraine. Sumatriptan been claimed to block the effects of trigeminal nerve stimulation.

The 5-HT_2 receptor family:

The 5-HT_2 receptor family consists of three subtypes termed 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. The latter site was previously termed 5-HT_{1C} before its structural similarity to the 5-HT_2 family members was recognised. All three are thought to be linked to the phosphoinositol hydrolysis signal transduction system via the a subunit of the Gq GTP binding protein, although it is yet to be proven that the 5-HT_{2B} receptor is so coupled in native tissue. Indeed, in human pulmonary artery endothelial cells, 5-HT_{2B} receptor stimulation causes intracellular calcium release via a mechanism independent of phosphatidylinositol hydrolysis.

5-HT_{2A}

This receptor (previously termed 5-HT_2) s widely distributed in peripheral tissues where it mediates contractile responses of many vascular, urinary, gastrointestinal and uterine smooth muscle preparations, platelet aggregation and increased capillary permeability in both rodent and human tissue. Centrally, it is principally located in the cortex, claustrum and basal ganglia. Stimulation of central 5-HT_{2A} receptors in rodents causes head shaking and may mediate the effects of hallucinogens such as lysergic acid diethylamide (LSD) in man, the release of glutamate from the rat cerebellum and the release of b-endorphin, corticosterone, luteinising hormone and prolactin as well as adrenaline from the rat adrenal medulla.

$5HT_{2A}$ receptor antagonists such as ritanserin are also reported to improve sleep quality. As the vasoconstrictor effects of 5-HT_{2A} receptor stimulation are markedly potentiated in

hypertension and atherosclerosis, while low levels of 5HT potentiate the thrombogenic and vasoconstrictor effects of other neurotransmitters, selective 5-HT_{2A} receptor antagonists, notably ketanserin, are in clinical use for hypertension.

5-HT_{2B}

This receptor mediates contraction of the rat stomach fundus and endothelium-dependent relaxation of the rat and cat jugular veins and possibly of the pig pulmonary artery, via nitric oxide release. In man, 5-HT_{2B} receptor mRNA is expressed in low levels in the brain, and at much higher levels in the placenta, lung, liver, kidney, heart, intestine and stomach. Recent receptor specific antibody studies in the rat have reported the presence of receptor protein in the amygdala, septum, hypothalamus and cerebellum. In rodent studies, stimulation of 5-HT_{2B} receptors has been reported to cause modest anxiolysis, hyperphagia and reduced grooming. They may also be involved in the precipitation of migraine and the action of the 5-HT_2 receptor antagonist migraine prophylactics, cyproheptadine, pizotifen and mianserin. The 5-HT_{2B} receptor has also been postulated to mediate mesenteric artery contraction in hypertensive, but not normotensive rats.

5-HT_{2C}

5-HT_{2C} specific antibodies have recently been used to show the presence of the receptor protein in the choroid plexus (highest density) and at a lower level in the cerebral cortex, hippocampus, striatum, and substantia nigra of rat and a similar distribution in man. There is, at present, no evidence of the existence of this receptor or its mRNA in peripheral tissues.

5-HT_{2C} receptors in the hippocampus may control appetite threshold: 5-HT_{2C} receptor deficient mice have hyperphagia, type 2 diabetes, and increased body weight (Nonogaki et al,1998) (Tecott et al, 1995) as well as epileptic seizures (Brennan et al,1997).

The 5-HT_3 receptor

The 5-HT_3 receptor binding site is widely distributed both centrally and peripherally and has been detected in a number of neuronally derived cells. The highest densities are found in the area postrema, nucleus tractus solitarius, substantia gelatinosa at all levels and nuclei of the lower brainstem such as the trigeminal nucleus and the dorsal vagal complex. It is also found in higher brain areas such as the cortex, hippocampus amygdala and medial habenula, but at lower densities. Peripherally, it is principally found on the neurones of the sensory and enteric nervous systems and pre-and postganglionic autonomic neurones. Unlike other 5-HT receptors, 5-HT_3 receptor subunits form a pentameric cation channel that is selectively permeable to Na^+, K^+ and Ca^{++} ions causing depolarization (Maricq et al, 1991).

In vivo, administration of 5-HT_3 receptor ligands can either stimulate or inhibit cardiac function, induce vasodilation, affect lung and intestinal function, cause pain and sensitisation of nociceptive neurons and induce nausea and vomiting. This latter action is thought to underlie the emetic side effects of cancer chemotherapy and radiotherapy and has led to the use of selective 5-HT_3 receptor antagonists as antiemetic agents. Central 5-HT_3 receptor antagonists are reported to have anxiolytic actions in some, but not all. 5-HT_3 receptor antagonists have also been reported to induce cognitive enhancing effects and to reduce dopamine function in rats suggesting utility as procognitive and antipsychotic agents. Highly potent and selective 5-HT_3 receptor antagonists include ondansetron, granisetron, tropisetron.

The 5-HT_4 receptor

This receptor is highly concentrated in areas of the rat brain associated with dopamine function such as the striatum, basal ganglia and nucleus accumbens where they may be located on GABAergic or cholinergic interneurons and/or on GABAergic projections to the substantia nigra. The receptor is functionally coupled via the G G-protein.

Peripherally, stimulation of 5-HT_4 receptors on the myenteric plexus of the guinea pig and rat oesophagus, and guinea pig and human colon cause contractions. Thus, 5-HT_4

receptor antagonists may be of use in irritable bowel syndrome. 5-HT_4 receptors in the mucosa of the rat colon and elsewhere are involved in secretory processes. They may also mediate vomiting in ferrets, possibly by activating vagal afferents. 5-HT_4 receptors in the heart induce tachycardia and positive inotropic effects when stimulated and may be of importance in cardiovascular pathology. 5-HT_4 receptor activation may also cause cortisol secretion and bladder contraction in man. Centrally, 5-HT_4 agonists can increase striatal dopamine release. In the rat frontal cortex, 5-HT_4 receptor stimulation facilitates acetylcholine release and may thus have cognition enhancing effects while in the hippocampus, it may result in increased 5-HT release, suggesting a possible role in the mediation of anxiety.

The first 5-HT_4 agonists reported were benzamides such as renzapride, cisapride and zacopride. Later, benzimidazolones were characterized. However, all have substantial affinity for the 5-HT_3 receptor.

5-HT_6 and 5-HT_7

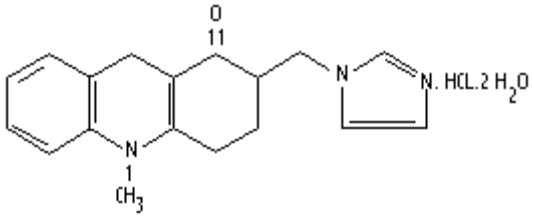
5-HT_6 and 5-HT_7 receptors stimulate cAMP synthesis. Tricyclic antidepressant drugs amytryptiline and clomipramine show high affinity for 5-HT_6 receptors, and clozapine displays high affinity for 5-HT_6 and 5-HT_7 receptors, indicating a potential involvement in their therapeutic action (Plassat et al, 1993) (Monsma et al, 1993). The 5-HT_7 receptor might also play a role in the regulation of mammalian circadian rhythms (Lovenberg et al, 1993).

V. Serotonin Receptor Antagonists as Antiemetics

1.ONDANSETRON

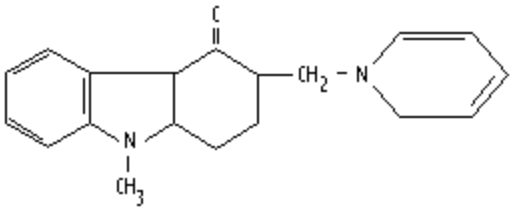
1. Chemical structure:

Ondansetron was synthesized in 1983 as hydrochloride dehydrate salt (fig.1). its structure is similar to that of 5-HT, both have an indole nucleus. It has one asymmetric center and al 1:1 racemic mixture of the D and L enantomers. Both isomers are selective antagonist at 5-HT_3 receptors.



Tetra hydro -9 methyl (-3 – (2 – methyl timidazol – 1 – (methyl)
-carbozol – y (9H) – one
C_{18} $H_{19}N_3O$ = 293.4
C_{18} $H_{19}N_3O$, HCl, 2 H_2O = 365.9 ondansetron hydrochloride
(Stewart, et al, 1996)

Ondansetron (Zofran, Cerenex, Pharmaceuticals, Research triangle Park, NC) (±) 1,2,3,9 – tetrahydro-9-methyl-3- [(2-methyl-lH-imidazol-1-yl) methyl] – 4H-carbazol-4-one monohydrochloride dehydrate). (morrow et al 1995).



2. Physical properties :

A white to off-white powder. Sparingly soluble in water and in alcohol, very slightly soluble in acetone, in chloroform and in ethyl acetate, slightly soluble in dichton methane and in isopropyl alcohol, soluble in methyl alcohol.

Store in airtight containers, protect from light.
(Hagan et al, 1996).

Ondansetron is stable under normal conditions for 4 years. It has a PKa of 7.4 and aqueous PH of 4.6. (Simpson and Hicks, 1996).

3. Mechanism of Action:

- It has been proposed that both cytotoxic drugs and radiation cause cellular damage, thereby releasing a number of chemical mediators including serotonin from the intestinal mucosa. This serotonin is thought to depolarize vagal afferent nerves in the gut, or sensitize them to other stimuli such as the mechanical effects of pulsatile blood flow. Vagal afferent excitation in turn elicits the vomiting reflex.

- Ondansetron antagonizes the depolarizing action of serotonin at $5HT_3R$ on vagal afferent nerves (Figure4).

- The drug blocks the Bezold – Jarisch reflex response (transient bradycardia and hypotension. (Milne and Heel, 1992; Markham and Sorkin, 1993; Tyers, 1992; Wolf, 2000; Scaratino et al. 1992).

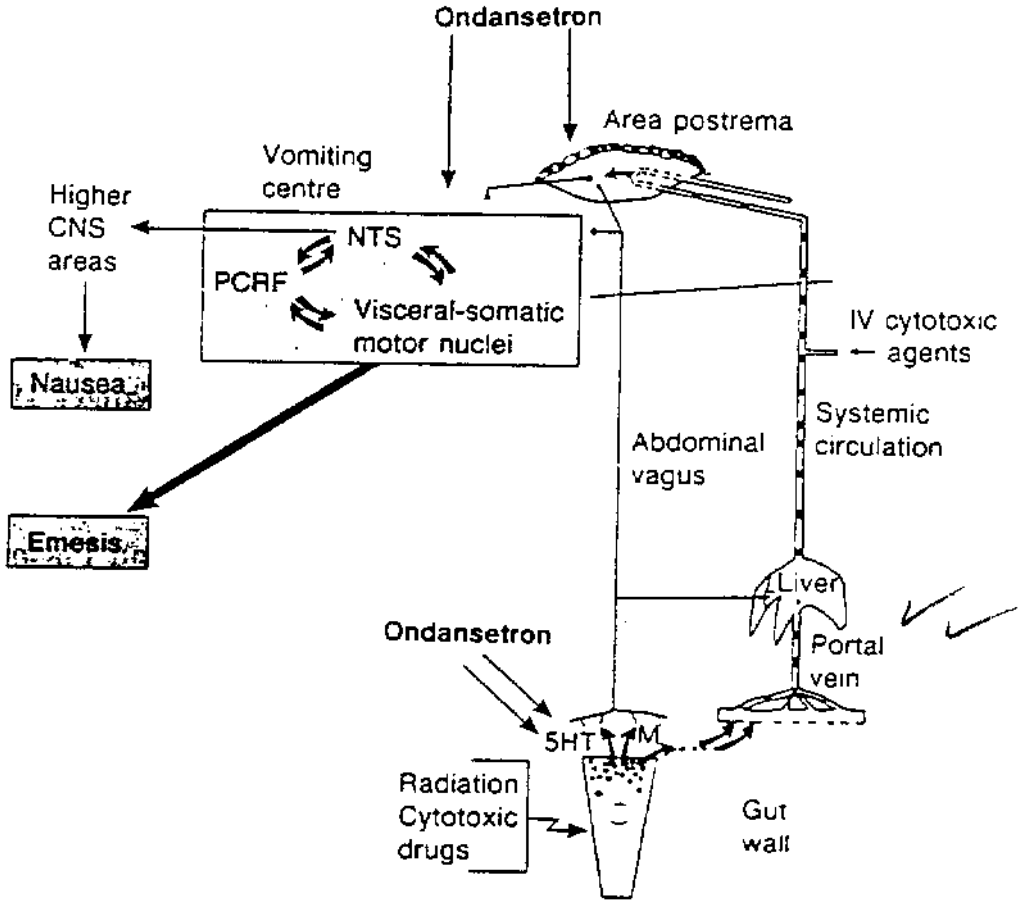


Figure 4. Proposed sites of the antiemetic action of ondansetron at 5-HT3 receptors located peripherally on vagal afferent fibres in the gut wall and centrally in the area potrema, nucleus tractus solitarius (NTS) and other associated brain areas; M= other chemical mediators; PCRF = parvicellular reticular formation (from Andrews et al. 1988; pratt et al. 1990).

4. Pharmacokinetics:

Absorption and Plasma concentration:

- Following oral administration, it is rapidly absorbed with peak plasma concentration of 33 mgl L were reached in 1 to 1.5 h after 8 mg.

- The bloavailability is about 60% due to hepatic first – pass metabolism, its estimated from area under the plasma concentration – time curve (AVC).

- Steady – state plasma concentration were maintained with continuous infusion.

- 70 – 76% protein bound

- volume of distribution is 160 L and the mean elimination half-life is 3h. (Gregory and Ettinger, 1998; Markham and Sorkin, 1993; Milne and Heel, 1991; Tyers, 1992; Scarantino et al., 1992).

Distribution :

Ondansetron is extensively distributed in the body, results in vitro suggest that about 70% to 75% of the drug in plasma is protein bound. The volume of distribution is large (IGOL) (Milne and Heel, 1991).

The apparent volume of distribution at steady state (Vss) in young healthy is approximately 1.8 L kg. $^{-1}$, which is greater than the 0.9 Lk5^{1} representing total body water. This reflects the high lipid solubility of Ondansetron, which has a Log D (octanol/water) of 1.3 at PH 7.4. Ondansetron is 67% ionized at blood PH. Protein binding is about 70% which does not greatly influence pharmacokinetics. Alph I acid

glycoprotein, which can change significantly in cancer, is not a major binding protein for ondansetron. The blood : plasma ratio of ondansetron is 0.833, implying that it distributes into red cells (Pritchard, 1992). The brain : plasma ratio in animals is less than 0.5, suggesting slow penetration into the CNS. This is supported by low cerebrospinal fluid (CSF) concentrations, about 10% of plasma concentration seen in man after oral dosing. (Simpson and Hicks, 1996).

Routes of Administration:

1. Intravenous route

- The time to reach peak plasma drug concentration Tmax = 7 min
- T ½ = 3 – 3.5h
- Total body clearance (CL) = 600 ml. min $^{-1}$

IV ondansetron provided more rapid onset of action than the oral route.

2. Oral route:

Ondansetron tablets are bioequivalent to the oral solution. It dissolves completely and quickly in-vivo (Pritchard, 1992)

- Well absorbed, with bioavailability of 60 to 70%. First pass metabolism removes 30 – 40% of the drug.
- The presence of food in GIT causes a small increase in the bioavailability.
- The use of antacids does not alter bioavailability

(Pirchard, 1992)

3. Intra muscular route:

The drug is rapidly absorbed with t½ = 5 - 10 min

(Simpson and Hicks, 1996)

4. Colonic route:

The t½ was comparable with that after oral dosing. C_{max} was reduced and the t½ prolonged to almost 7h. Bioavailability (79%) was not significantly different from that after oral administration. Ondansetron is absorbed as well in the colon as it is in the upper GIT. Dose modification is unnecessary after bowl resection.

5. Rectal route:

T_{max}, C_{max}, and t½ were similar to those after clonic administration.

6. Sublingual and subcutaneous routes:

The lipophilicity of ondansetron suggest that sublingual or subcutaneous administration would result in good absorption.

Table 4.Pharmacokinetic data after different routes of ondansetron administration in healthy volunteers

	Oral 8 mg single dose Mean (95% CI)	Oral steady state Mean (95% CI)	Intravenous 8 mg 5 min infusion Mean (s.d.)	Intramucular 4 mg single dose Median (range)	Colonic 8 mg infusion Mean (s.d.)	Rectal 8 mg single dose Mean (s.d.)
T_{max} (h)	1-0* (0.8-2.0)	1.0* (0.8-1.5)	0.12 (0.05)	- (0.08-0.17)	1.1 (0.3)	1.3 (0.7)
C_{max} (ng mL^{-1})	31.2 (25.6-38.1)	38.9 (31.2-48.4)	80 (33.0)	24 (12-30)	28 (13.0)	26 (14.0)
t½ (h)	3.2 (2.4-5.8)	3.3 (3.3-8.1)	2.8 (0.6)	- -	6.9 (1.4)	6.8 (0.9)
CL (mL min^{-1})	-	-	702 (167)	-	-	-
AUC (ng h^{-1} mL^{-1})	-	130.3 (106.0-160.2)	-	- (103)	236 (64)	180

* Median (range)

4. Metabolism and Elimination:

- Metabolism:

  The major clearance of ondansetron (95%) is by hepatic metabolism (Pritchard, 1992). The enzyme system involved are cytochrome P450, particularly CYP2D6 and CYP3A (Fischer et al., 1994). 6-hydroxylation and demthylation are minor routes of metabolism. Forty percent of ondansetron is metabolized to the active compound 8-hydroxyondansetron which is not detected in plasma as it is rapidly conjugated in Liver. It does not contributed to the activity of the parent drug. (Simpson and Hicks, 1996).

The drugs are metabolized by different subtype of cytochrome P450 enzyme system, ondansetron metabolized mainly by the ubiquitous cytochrome P450-3A subtype. (Wolf, 2000).

Inducers or Inhibitors of P2D6 enzymes may change the clearance and half life of ondansetron. Ondansetron do not induce or inihit the cytochrom P450 enzyme system (Roussel, 1997; Sanwald et al., 1996).

- Clearance:

  Renal clearance of the parent drug represents less than 5% of total plasma clearance.

  Ondansetron does not appear to be a flow – dependent drug since changes in hepatic blood flow would not be expected to result in much changes in ondansetron clearance. (Pritchard, 1992).

  Plasma clearance is approximately 40% of hepatic blood flow. (Lazarus, et al. 1990). Ondansetron is extensively metabolized with only 5% recovered in the urine as unchanged drug. The primary metabolic pathway is hydroxylation of the indole ring followed by glucuronide or sulfate conjugation. (Otaxo Wellcome, 1996).

- Excretion:

  Following intravenous administration of radio labeled ondansetron more than 60% of its metabolites are excreted in urine, the remainder are found in palces. As lipophilic drug, which diffuses easily, ondansetron will probably pass across placenta and into milk; there are, however, no published data on these phenomena. Ondansetron is not recommended during pregnancy and lactation. (Simpson and Hicks, 1996).

Factors Affecting Ondansetron Pharmacokinetics:

1. Elderly:

   May be prone to accumulation of ondansetron if prolonged dosing with frequent dosing intervals are used. Dose modification is not recommended for elderly because age accounts for small part only of variability in clearance. (Simpson and Hicks, 1996).

2. Children:

   T½ is shorter in young children reflecting a greater rate of elimination. (Simpson and Hicks, 1996).

3. Gender:

   There is some evidence that clearance is slower in females of similar age even when body weight is taken into account (Pritchard 1992). Females show higher bioavailability after oral doses. (Simpson and Hicks, 1996).

4. Circardian Rythms:

   Absorption was highest after the morning dose and declining by 15% by night time dose. C_{max} was significantly lower and T_{max} more prolonged as day progress. (Simpson and Hicks, 1996).

5. Renal failure:

   Less than 5% of drug is excreted in urine, therefore adjustment of dosing is unnecessary for patients with renal problems. (Amentea et al, 1993).

6. Liver disease:

Figg, et al, (1992) have studied the effect of liver disease on pharmacokinetic of ondansetron, the Vd was unchanged, no effect on mental state, the clearance was prolonged, ranging from 10h fro mild liver disease to 20h in severe cases.

There was increase in bioavailability and C_{max} similar results were obtained by others. (Black, et al. 1993).

Figure 5. Metabolism of ondansetron in humans. Major, > 20% of dose; minor, <20% of dose; very minor, <5% of dose.

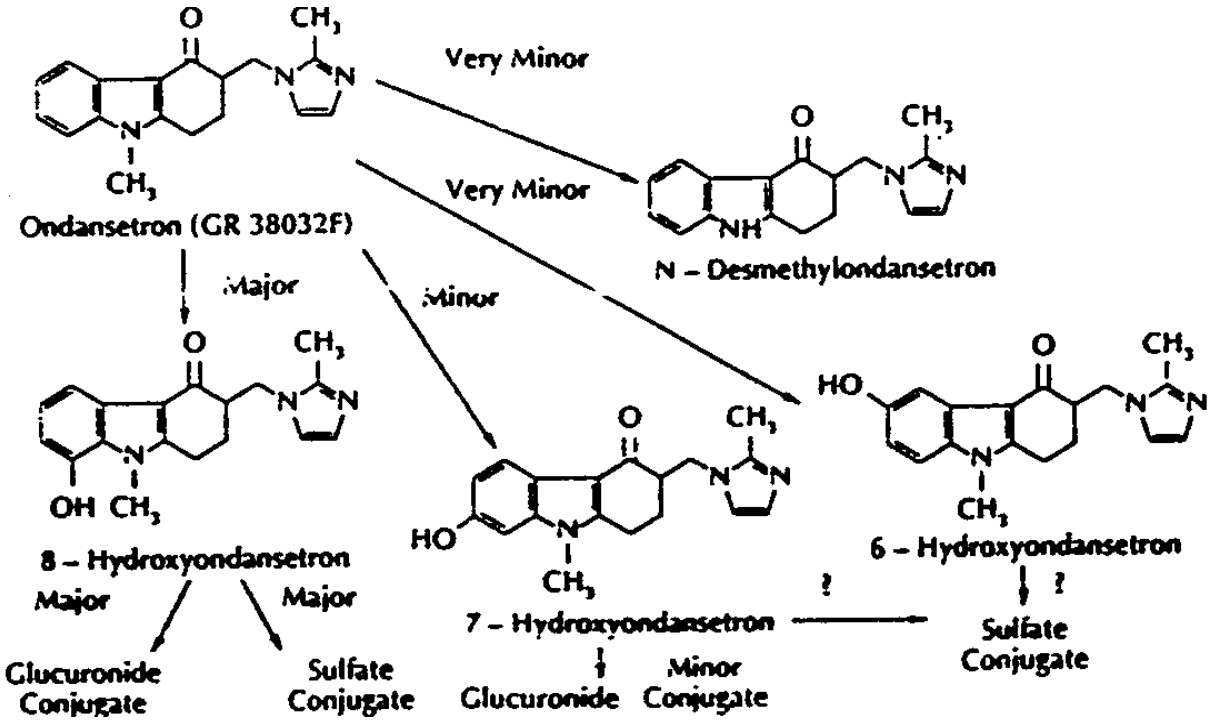


Table 5. In Vitro Pharmacologic Activity of Ondansetron Metabolites

		Von Bezoid-Jansch Reflex in the Cat (30 µ/kg IV)		
	Pki (^{3}H) GR65630 Binding*	Onset (min)	Duration (min)	Peak Dose Ratio
Ondansetron	8.5	<1	76	>13
8-Hydroxyondansetron	8.7	<1	90	>20
7- Hydroxyondansetron	7.3	-	-	-
6- Hydroxyondansetron	6.4	<1	16	>20
N-Desmethylondansetron	6.5	<1	13	-

*(^{3}H) GR65630 is a radiolabelled ligand for the 5-HT_3 receptor. The ability to displace GR65630 from the receptor is decendent on the affinity of the test compound to the receptor. A pki of 8.5 means that at a concentration of $10^{-8.5}$ mol/L, half of the GR65630 has been displaced. The lower the concentration of test compound (hence higher pki) the higher the affinity for the 5-HT_3 receptor.

6. Pharmacological Action :

1. Effect on CNS:

- No Extrapyramidal reactions. (Halperin and Murphy, 1992)
- It antagonize the overstimulation of central sertonergic receptors in Psychosis, which is manifested mainly by visual hallucinosis, paranoid delusions, and confusion, is a common complication in patient with advanced Parkinson's disease. (Zoldan et al. 1995).
- It causes tonic-clonic movements and forting.
- It has dose – dependent anxiolytic action with onset after several days of therapy but possibly influence only relatively low level of anxiety. (Wolf, 2000).

2. Effect on CVS:

- It has minor and usually clinically unimportant effects on cardiac electrophysiologic behavior.
- It causes slight QT prolongation, reduced heart rate, conduction disorders (AV block) during treatment and arrhythmias. (wolf, 2000).

3. Effect on GIT:

- It reduces incidence of emetic episodes by blocking serotonin – induced depolarization of vagal afferent nerves which in turn induce nausea and vomiting via reflex activation.
- It prolongs colonic transit but has no major effect on small intestinal transit time. (Markham and Sorkin, 1993).

4. Effect on Liver:

- It may produce transient increase in transaminase enzymes.

- It increases bilirubin, hyperlilirubinaemia was unusual and usually limited between 2 to 3 times baseline values. (Verrill and Judson, 1994; Grunberg, 1992).
- Transaminases returned to normal after treatment and were not associated with any clinical problems. It is difficult to separate the effect of cancer and concomitant treatments from those of ondansetron. (Simpson and Hicks, 1996).

7. Adverse effect and Precautions:

1. Effect on CNS:
   - Most common adverse effect is headache (the severity is not dose related).
   - Sensation of flushing or warmth.
   - Dizziness, anxiety and sedation.

2. On CVS:
   - Chest pain.
   - Tachycardia and bradycardia.
   - Hypotension.

3. On GIT:
   - Constipation, diarrhea.
   - Dry mouth.
   - Transient rise in liver enzymes.

4. Anaphylactacid – Anaphylactic Reactions:

Its characterized by urticuria, angiodema, hypotension, bronchospasm and dysnea. May be due to I.V. administration of ondansetron (Chen et al, 1993).

5. Hypersensitivity reactions:

Hypothesis of etiology is class effect rather than a drug-specific hypersensitivity. So, the suspected drug should be discontinued, in addition avoid administration of another $5HT_3$ antagonist, as replacement in circumstances where the patient has previously experienced even a mild hypersensitivity type reaction with another $5HT_3$ receptor antagonist.

Table 6.Frequency of Adverse Events with Ondansetron

Dose Level (mg/kg)	Mild Sedation	Headache	Elevated Transaminase	Dizziness	Dry Mouth	Patient at Risk
0.04-0.125	5	1	1	0	3	15
0.15	8	8	7	3	5	14
0.18	2	1	1	1	0	4
0.2-0.35	4	5	6	1	0	13
Total	**19(41%)**	**15(33%)**	**15(33%)**	**15(11%)**	**8(17%)**	**46**

8. Therapeutic uses:

1. Chemotherapy – induced emesis (CTNV)
2. Radiogenic emesis (RTNV)
3. Postoperative nausea and vomiting (PONV)

Non-registered indications:

1. Other forms of emesis and nausea. Eg:
    - To treat hyper emesis gravidarum
    - Vomiting due to intoxication
    - Management of PCP with cortimoxazole

- Vomiting associated with craino-cerebral trauma
- Ineffective in kinetoses or morphine – induced nausea.

2. Diarrhea – predominant irritable bowel syndrome.
3. Dose-dependent anxiolytic action with onset of action several days of therapy.
4. Antipsychotic effect (Parkinson psychosis and schizophrenia).
5. Alcohol and drug abuse.
6. Cognitive functions.
7. Nociception, migraine. (Wolf, 2000).

Ondansetron is used in the treatment of Panic disorder. To date, ondansetron is the most pharmacologically specific anti-panic agent to be developed. (Schneier, et al, 2001).

Reinfusion of autologous hematopietic peripheral blood stem cells (PBSC) or bone marrow is often accompanied by flushing, dyspnea, abdominal cramping, nausea and vomiting, diarrhea. These symptoms and the observation that they can be prevented by ondansetron, led to the assumption that these side-effects are due to infusion of free serotonin during the reinfusion of PBSC or bone marrow. (Wymenga et al. 1999).

Ondansetron has been introduced to clinical practice as antiemetic for cancer treatment – induced and anesthesia related nausea and vomiting. Its use under these circumstances is both prophylactic and therapeutic. (Yejh et al., 2000).

9. Toxicity:

The toxicity is low, there is no evidence of mutagenic or teratonigenic effects or specific organ toxicities. Only in long-term studies using higher dosages have rodents exhibited liver parenchymal changes of the type often observed on administration of drugs metabolized by the cyt P450 system.

In healthy volunteers $5HT_3$ receptor antagonists are well tolerated over a very wide dose range. Only at multiples of clinical dose levels do signs of intoxication occur, for example in the form of visual and acoustic hallucination. (Wolf, 2000).

10. Drug Interactions:

1. Antibacterials : Rifampicin pretreatment reduced the area under the plasma concentration time curve of oral ondansetron by 55% and IV ondansetron by 48% concomitant use of rifampicin or other potent inuducers of cytochrome P450 iso enzyme CYP3AY, with ondansetron may reduce antiemetic efficacy. (Villikkak. Et al, 1999).

2. Sytochrome P450 inducers: e.g. Phenobarbital or phenyl butazone increase break down of ondansetron so decrease its therapeutic effect.

3. Cyt P450 inhibitors such such as cimetidine have no revelent influence on the plasma concentration of drug. (Wolf, 2000).

4. Opiod analgesic:

   As morphine, elimination of ondansetron was prolonged but it may be due to posoeperative changes in physiology rather than use of opioid.

5. Alcohol:

   Ondansetron may reduce some effects of alcohol, but not affecting absorption of it.

6. Smoking:

   As smoking induce hepatic enzymes it may increase the clearance of ondansetron, no dose adjustment is recommended.

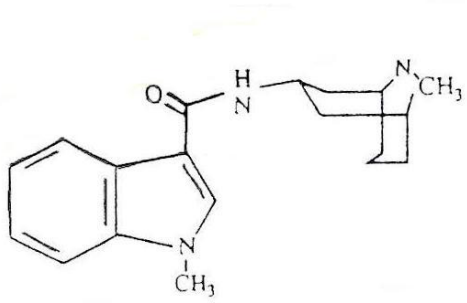
7. Pyridostigmine:

Ondansetron increases the activity of compound. (Simpson and Hicks, 1996).

GRANISETRON

1- Chemical Structure:

Endo-N-[9-methyle-9-azabicyclo-(3.3.1) non-3-yl] 1-methyl-1H-endole-3-carboxamide (Yarker and McTavish, 1994) (Adams and Vally 1996).



$C_{18}\ H_{24}\ N_4\ O$

(Figure 6: Chemical Structure of Granisetron)

(Andrews P, 1994)

2- Physical Properties:

Granisetron Hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20%. Granisetron hydrochloride injection is clear, colorless solution for intravenous administration.

Granisetron tablets (Kytril) for oral administration are triangular, white biconvex and film coated.

3- Mechanism of Action:

The exact mechanism of Granisetron for the prevention of postoperative nausea and vomiting remains unclear, but it has been suggested that this drug may act on sites containing serotonin type 3 receptors with demonstrated antiemetic effects.(Carmichael et al, 1989)

Granisetron is a Potent and highly selective antagonist of 5-HT3 receptors. In vitro studies have demonstrated that Granisetron has a high affinity and selectivity for 5-HT3 binding sites in a variety of tissues, including those in some areas mediating emesis (Plosker and Goa, 1991) (Leslie et al, 1990).

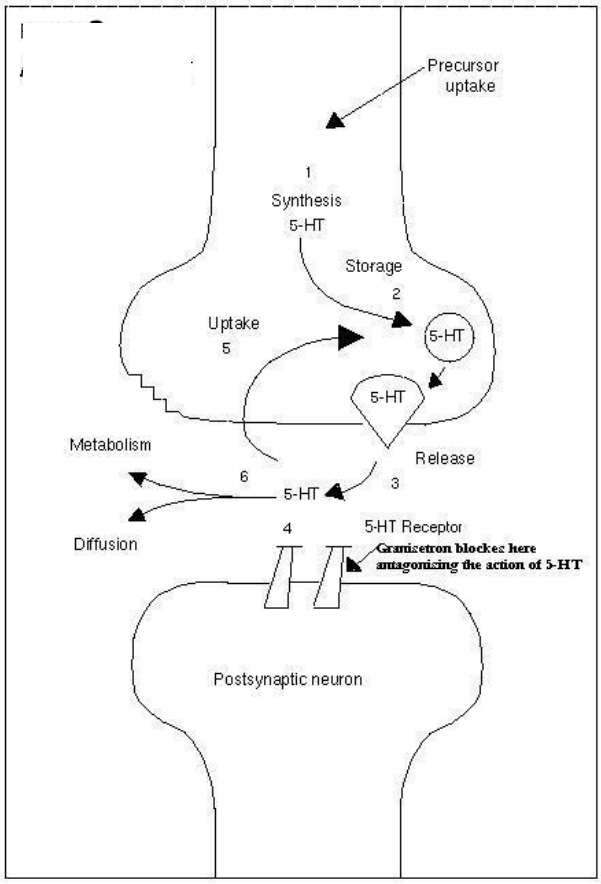


Figure 7. site of action of serotonin receptor antagonists.

4- Pharmacokinetics:

Absorption:

Granisetron is well absorbed orally with peak plasma concentration occurring about 2 hours after a dose. It was reported to be more potent as antiemetic when administrated by the oral route than the intravenous route (Fitzpatrick et al, 1990).

Distribution and Bioavailability:

Granisetron has been shown to be widely distributed and rapidly eliminated primarily by hepatic metabolism (Upward et al, 1990). It is widely distributed both in healthy volunteers and in cancer patients (Zussman et al, 1988).

Oral bioavailability of Granisetron is about 60% as a result of first-pass hepatic metabolism .

It has a large volume of distribution of around 3 litres per Kg. Plasma protein binding is about 65%.

Metabolism :

the pharmacokinetics of Granisetron exhibit considerable interindividual variation, and the elimination half-life is reported to be around 3 to 4 hours in healthy subjects but about 9 to 12 hours in cancer patients.(Yarker and McTavish, 1994) (Adams and Vally, 1996).

Granisetron in comparison to other 5-HT receptor antagonists, is supported by the longer plasma half-life. (Carmichael et al, 1998), the t1/2 for granisetron in Westren studies was approximately 4 to 5 hours in healthy volunteers and 9 to 12 hours in cancer patients (Yarker and McTavish. 1994) (adams and Vally, 1996). Such differences between patients with malignancies and healthy volunteers are common and may potentially be caused by one of several underlying factors. These factors include differences in elimination caused by the underlying malignancy, possible drug interactions with cytotoxic chemotherapeutics, or changes in the binding characteristics of plasma proteins (Addelman et al, 1990).

It’s metabolized in the liver by N-demethylation and aromatic ring oxidation followed by conjugation. Animal studies suggest that some of the metabolites have 5-HT3 receptor antagonist activity.

Granisetron is metabolized by the cytochrome P 2D6 isoenzyme of the hepatic cytochrome P-450 enzyme system. Inducers or inhibitors of these enzymes may change the clearance and the half-life of these serotonin antagonists (Sanwald et al, 1996).

Excretion:

In normal volunteers, approximately 12% Is eliminated unchanged in the urine in 48 hours, the reminder is excreted as metabolites 49% in urine and 34% in the feces (Balfour and Goa, 1007).

Granisetron clearance is not affected by renal impairment, but is lower in the elderly and in patients with hepatic impairment (Yarker and McTavish, 1994) (adams and Vally, 1996).

The fact that the pharmacokinetics of Granisetron have not been adequetly studied in children has been replaced with “A pharmacokinetic study in pediatric cancer patients (2 to 16 years of age), given a single 40 mcg/kg intravenous dose of kytri injection, showed that volume of distribution and total clearance increased with age. No relationship with age was observed for peak plasma concentration or terminal phase plasma half-life. When volume of distribution and total clearance are adjusted for body weight, the pharmacokinetics of Granisetron are similar in pediatric and adult cancer patients” (SmithKline Beecham, 1997).

5- Pharmacodynamics :

Granisetron is more selective to 5-HT3 receptors and this can be relevant for efficacy. It has a selectivity ratio of approximately 1000:1 for the 5-HT3 receptors with respect to any other type of receptor (Freeman et al, 1992) (Marr et al, 1991).

Granisetron is an antiemetic and antinauseant agent which exerts its activity via selective antagonism of serotonin$_3$ receptors. it probably exerts its effects on acute emesis (i.e. episodes occurring within 24 hours of cytotoxic therapy) by acting at both periphral and central sites. Peripherally it probably blocks serotonin-evoked stimulation of vagal afferent nerves from the gastrointestinal tract; centrally it probably bloks stimulation of 5-HT3 receptors in the chemoreceptor trigger zone and the nucleus of tractus solitarius of the brainstem, both of which activate the vomiting reflex.

Radioligand binding techniques show that Granisetron has a strong affinity for central 5-HT3 recognition sites in the brain (Seynaeve et al, 1991). The highest density of these sites in the nucleus of the tractus solitarius, the main terminus for vagal afferent fibers originating from the gastrointestinal tract (Leslie et al, 1990) (Pratt et al, 1990). Another major site of 5-HT3 receptors is in and around the area postrema of the medulla oblehngata, which is the site of the chemoreceptor trigger zone for emesis (Plosker and Goa, 1991).

The selectivity of granisetrin for 5-HT3 receptors has been demonstrated in the rat. Granisetron lacks any significant interaction with 5-HT$_{1A-D}$, 5-HT$_2$, 5-HT$_4$, dopamine D$_1$ or D$_2$, histamine H$_1$, benzodiazepine, picrotoxin, or α_1-α_2, or βreceptor binding sites (Fake et al, 1987) (Sanger and Nelson, 1989) (Freeman et al, 1992) (Andrews, 1994). Studies in rat and guinea-pig brain have shown that the affinity of Granisetron for 5-HT3 receptors is 4,000 to 40,000 times greater than for any other receptor type studied (Blower, 1990). In addition, Granisetron has been reported to be more potent and longer acting than ondansetron (Andrews, 1992).

Some serotonergic pathways are thought to be involved in the control of anxiety and several animal studies have investigated the potential anxiolytic effects of Granisetron and other 5-HT3 antagonists. However, these studies have yielded equivocal results and anxiolytic activity, where observed, has been inferior to that of antianxiety

agents such as diazepam and buspirone (Nevins and Anthony, 1994) (Higgins et al, 1991).

It has also been postulated that 5-HT3 antagonists may possess antipsychotic activity through their action at central sites and there is some evidence to suggest that these agents, including Granisetron, can attenuate hyperactivity of dopaminergic neurons in the mesolimbic area of the rat brain (Costall et al, 1990).

Granisetron effects on the heart are not very significant. However, small ECG changes (e,g. increase in the PR, QRS, and QTc intervals) have been recorded. These changes, which generally occur within a few hours of drug administration, were transient, and were not associated with clinical symptoms (Steven and Bernard, 1997).

6- Therapeutic Uses:

Prophylactic parentral or oral administration of Granisetron reduces the incidence of, or completely prevents, nausea and vomiting induced by cytotoxic drugs (including the highly emetogenic drug cisplatin) and is an effective intervention therapy where emesis is already occurring. Granisetron is also effective in the prevention and treatment of radiation-induced emesis, at doses similar to those used to control the chemotherapy-induced condition.

Granisetron is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of postoperative nausea and vomiting (Maisano et al, 1995).

Granisetron hydrochloride is effective for the treatment of emesis in patient receiving cytotoxic drugs. (Bermudez et al, 1988). It is more potent and has longer-acting properties against cisplatin-induced emesis than Ondansetron. (Andrews et al, 1992)

It has been demonstrated that this drug reduces the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. (Fujii et al, 1997).

The two commercially available 5-HT3 (serotonin) receptor antagonists, Ondansetron and Granisetron, have been shown to be highly effective in controlling the acute emesis associated with cisplatin (Perez, 1995) (Navari et al, 1995) (Tabona, 1990), particularly when administered along with a corticosteroid (e.g. dexamethasone) (Smyth et al, 1991) (Hesketh et al, 1994).

Granisetron is an effective antiemetic in children undergoing highly emetogenic chemotherapy, and effectively controls radiotherapy-induced and postoperative nausea and vomiting (Yarker and McTavish. 1994).

7- Adverse Effects:

Side effects of granisetron are not common, but they can occur and are generally well tolerated.

Granisetron appears to be well tolerated in clinical trials. Headache is the most frequently reported adverse event, occurring in about 14% of patients. Other less common adverse events associated with Granisetron administration include constipation, diarrhea, asthenia and somnolence.

Table 7: Adverse events occurring in more than 5% of patients

A/E	**Granisetron dose**		
	2 µg/kg	10 µg/kg	40 µg/kg
Headache	11.5%	7.7%	9.4%
Anaemia	5.8%	1.9%	0
Hypertension	5.8%	3.8%	5.7%
Constipation	5.8%	3.8%	0
Diarrhea	3.8%	5.8%	5.7%

Quoted from: (Riviere et al, 1994).

However, Granisetron does not cause the sedative, dysphoric, and extrapyramidal symptoms associated with nonserotonin type3 receptor antagonists (e.g droperidol, metoclopramide) (Watcha and White, 1992) (Yarker and McTavish, 1994). Adverse effects due to granisetron are considered to be clinically not serious (Fujii et al, 2001).

Granisetron also did not appear to affect Psychometric performance (Leigh et al, 1991) or EEG (Link et al, 1991) in human volunteers.

8- Safety and Tolerability:

Granisetron has an excellent safety profile(Aapro, 1991). Dose as high as seven times the normal clinical dose (i.e. up to 300 µg/kg) cause no major toxicity (Arnold, 1990). There are no reports attributed directly to granisetron of extrapyramidal reactions.

Headache and constipation are the most frequent side effects of granisetron; the former is treatable with simple analgesics, and the latter often resolves spontaneously (Tabona, 1990).

The use of Granisetron in children does not appear to affect its tolerability profile, nor does the use of repeated doses of Granisetron over up to 8 cycles of chemotherapy.

9- Toxicity of Granisetron:

Regarding toxicity, granisetron was considered safe throughout the studies reviewed. Most of these studies reported the well known toxicities of serotonin antagonist medications such as headache, constipation and diarrhea, and less frequently, sedation. In most studies, these toxicities occurred at similar rates with both antiemetic drugs (Perez et al, 1998).

10- Contraindications:

Hypersensitivity: hypersensitivity to this medicine is considered a contraindication of its use.

Pregnancy: Granisetron has not been studied in pregnant women, however, it has not been shown to cause birth defects or other problems in animal studies.

Breast feeding: it is not known whether Granisetron passes into breast milk. Although most medicines pass into breast milk in small amounts, many of them may be used safely while breast-feeding.

Children: in effective doses, Granisetron has not been shown to cause different side effects or problems than it does in adults (Yarker and McTavish. 1994).

Older adults: this medicine has been tested in a limited number of patients 65 years of age or older and has not been shown to cause different side effects or problems in older people than it does in younger adults. Granisetron was well tolerated by Patients regardless of hepatic function and no serious treatment-related adverse events were reported (Robert P, 1994).

11- Drug Interactions:

Coadministration of intravenous Granisetron and lorazepam has revealed no evidence of pharmacodynamic interactions (Leigh et al, 1991) (Link et al, 1991). In addition, no unwanted synergistic effects have been reported following coadministration of haloperidol and Granisetron (Leigh et al, 1992). In fact, the potential of Granisetron to modify the cytochrome P450 hepatic enzyme system has been reported to be low, suggesting that drug-drug interactions mediated by this system (the most common route of drug elimination) would be low (Bloomer et al, 1993).

DOLASETRON

Dolasetron mesylate (Anzemet, MDL 73, 147 EF) is a highly potent and highly selective 5-hydroxytryptamine (5-HT_3) receptor antagonist. (Coppes et al, 1999) that is under investigation as an antiemetic agent (Lerman et al, 1996).

1. Chemical Structure:

Chemically dolasetron mesylate (1H-indole-3-carboxylic acid-trans-octahydro-3-oxo-2, 6-methano-2H-quinolizin-8-yl ester,methanesulphonate) is a novel pseudopelletierine derivative (Boeijinga et al, 1992).

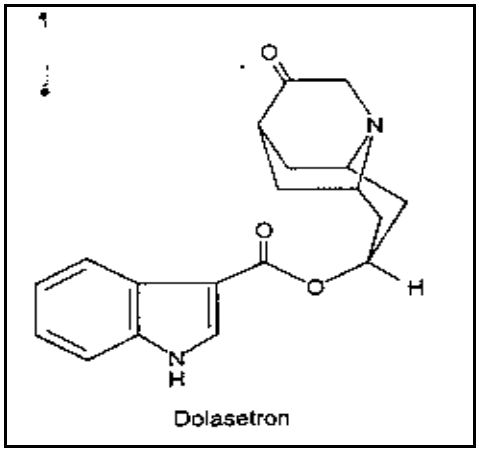


Figure 8. Chemical structure of Dolasetron

The empirical formula is:

$C_{19}H_{20}N_2O_3.CH_4O_3S$. (Lerman et al, 1996)

Molecular weight:

438.5 $gm.mol^{-1}$ (Lerman et al, 1996)

2. Physical properties:

It is a white to off-white powder that is freely soluble in water and propylene glycol, slightly soluble in ethanol and normal saline.

3. Pharmacokinetics:

Absorption and distribution:

- Dolasetron is rapidly absorbed after oral administration (Dempsey et al, 1996).
- It is administered as the monohydrate of its mesylate salt (Boxenbaum et al, 1993).
- Oral bioavailability of the tablet formulation was:

  Approximately 80 % in young women (Keung et al, 1995).

  70 % in young men (Boxenbaum et al, 1993).

  59 % in children (Lerman et al, 1996).
- Food intake didn't affect the pharmacokinetics disposition of orally administered. (Huebert et al, 1994).
- It is widely distributed in the body with the mean distribution volume is 4.15 to 5.5 L/kg. (Balfour and Goa, 1997)
- 69% to 77% of hydrodolasetron is bound to plasma protein.

  (Lerman et al, 1996)
- The half-life ($t_{1/2}$) of dolasetron mesylate in adult is less than 15 minutes after either oral or intravenous administration, whereas the half life ($t_{1/2}$) of its primary metabolite (hydrodolasetron) is approximately 8 hours.

  (Lerman et al, 1996)

Metabolism and elimination:

- After intravenous or oral administration, dolasetron undergoes rapid and complete reduction of the keton ring by carbonyl reductases to hydrodolasetron (MDL, 74, 156) (Stubbs et al, 1997) which is produced within 10 minutes of administration of dolasetron mesylate (Lerman et al,

1996) and has a potency approximately 50 times greater than that of the parent compound (Dempsey et al,1996).

- Hydrodolasetron (1H-indole-3-carboxylic acid,trans-octahydro-3-hydroxy-2,6- methano-2H-quinolizin-8-yl ester) (Boeijinga et al 1992) .

- Molecular weight of hydrodolasetron is 326.39 gm.mol^{-1} (Lerman et al, 1996).

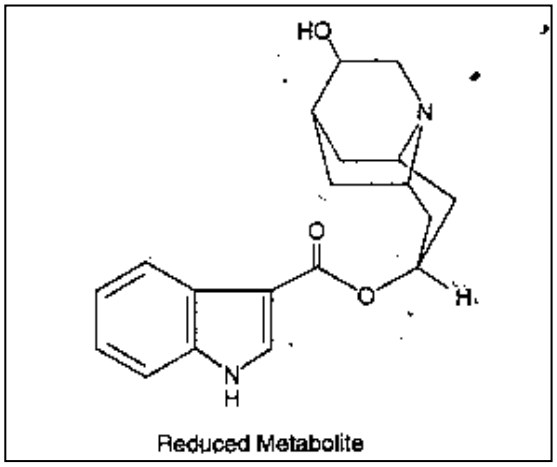


Figure 9. Chemical structure of Hydrodolasetron

- Peak plasma concentration (C_{max}) of hydrodolasetron occurred approximately 0.5

to 0.6 hours after intravenous administration and 1 hour after oral administration. (Balfour and Goa, 1997).

- Dolasetron has both renal and hepatic elimination mechanism (Stubbs et al, 1997) but less than 1 % of the dose is excreted in urine (Boxenbaum et al, 1993) while its metabolites are excreted in urine almost completely within 24 hours of administration (Dempsey et al, 1996).

Dolasetron undergoes complete biotransformation:

First step:

Rapid and complete reduction of the ketone ring by carbonyl reductases to hydrodolasetron.

Second step:

The majority of hydrodolasetron is excreted unchanged or undergoes glucuronidation. An alternate pathway for this metabolite, which accounts for approximately one-third of dolasetron metabolism, is hydroxylation at the 5'-hydroxy hydrodolasetron and 6'-hydroxy hydrodolasetron (Stubbs et al, 1997).

Cytochrome P_{450}2D6 (CYP II D6) has been identified as the isoenzyme responsible for the oxidation of hydrodolasetron. (Sanwald et al, 1996)

Third step:

The hydroxylated products are then excreted unchanged or metabolized further to yield sulfate or glucuronide conjugates.

Hydrodolasetron may also undergo N-oxidation, which is mediated by flavin monoxygenase and P_{450}3A (CYPIIIA), but this metabolite contributes less than 1% of the total dose. (Stubb et al, 1997)

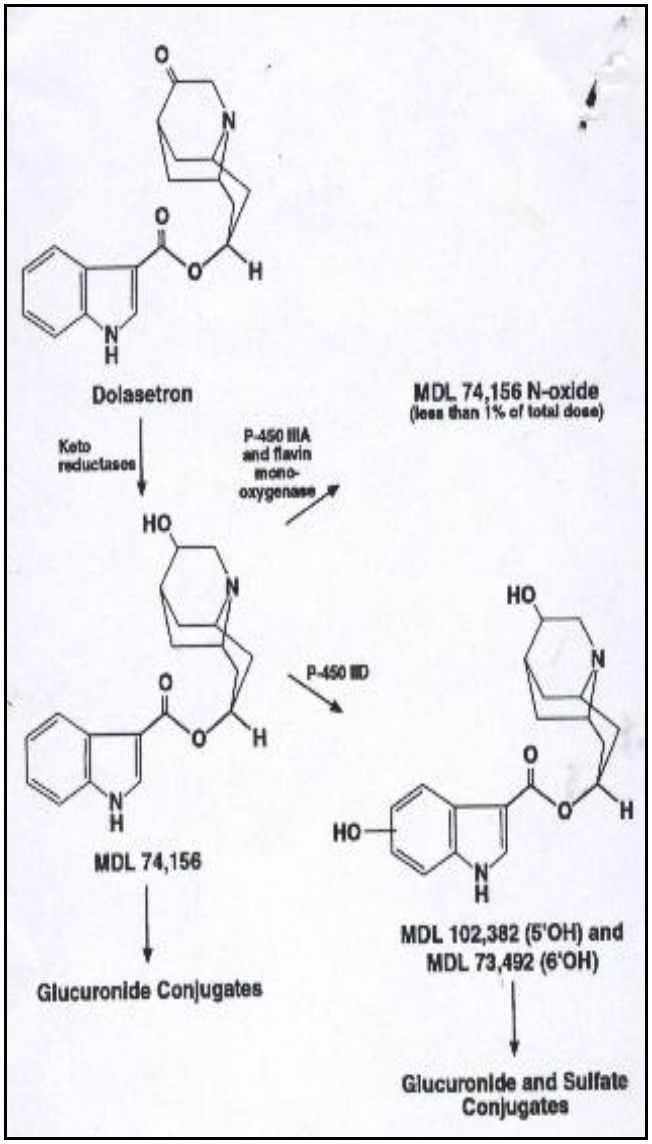


Figure 10. Biotransformation of Dolasetron

4. Pharmacodynamic:

1) Dolasetron induce its antiemetic effects by blocking 5-HT_3 receptors in medullary chemoreceptors trigger zone (CTZ) and in the gastrointestinal tract. (Balfour and Goa,1997)

2) In the central nervous system:
   - It has antipsychotic-like activity reduction on the dopamine neuron that produced a significant reduction in the number of spontaneously active dopamine neurons in the substantia nigra (A_9) and ventral tegemental area (A_{10}). (Sorensen et al, 1990)

   - It displaces [^{3}H] (S) _ zacopride from homogenates of entorhinal cortex (Barnes et al, 1990).

   - It has little, if any, affinity for α_1-α_2 and β_1-adrenergic receptors, 5-$HT_{1A,}$ 5-$HT_{1B,}$ 5-HT_2, benzodiazepine receptors and histamine receptors (Kortlila,1997).

3) In peripheral nervous system:

   It blocks the Von-Bezold-Jarisch reflex (transient bradycardia) induced by intravenous injection of 5-HT. (Boeijinga et al, 1992).

4) Dose of 10, 20 and 30 mg caused inhibition of the skin flare response to introdermal serotonin. (Merrouche et al, 1994)

5) It has electrophysiological effects:

- It decreased the maximum depolarization rate during the early phase of the action potential in guinea pig papillary muscle fibers without significantly affecting the duration of action potential.
- It produced minor changes in ECG intervals (prolongation of PR interval, QTC and QRS duration) and slightly increase heart rate (Balfour and Goa, 1997).

5. Therapeutic uses:

1- Prevention of chemotherapy-induced nausea and vomiting (CINV): (Korttila et al, 1997)

Single intravenous or oral doses of dolasetron is effective in preventing acute CINV. The optimum intravenous dose is 1.8mg/kg (Balfour and Goa,1997) which has superior efficacy and equal safety compared with lower doses of dolasetron and very similar efficacy compared with higher dolasetron mesylate doses(Hesketh et al,1996).

This achieved complete response in approximately 50% of patients who receiving highly emetogenic (cisptalin) chemotherapy and 60% to 80% of those receiving moderately emetogenic chemotherapy (Balfour and Goa,1997).

2- Prevention of radiotherapy-induced nausea and vomiting (RINV):

Dolasetron has also efficacy in preventing nausea and vomiting induced by fractionated or unfractionated radiotherapy or total body irradiation. A complete response rate of 100% is obtained with dolasetron 40mg intravenously and a dosage of 0.3mg/kg is superior to placebo (Balfour and Goa,1997).

3- Prevention of postoperative nausea and vomiting (PONV): (Korttila et al,1997)

Intravenous or oral dolasetron ranging from 12.5 to 100mg and 25 to 200mg,respectively (Balfour and Goa,1997).

4- Prevention of postanesthetic shivering: (Piper et al,2002)

A large dose of dolasetron(1mg/kg) is effective in preventing postanesthetic shivering (Bock et al,1999).

5- It is used as prophylaxis:

Dolasetron was administered orally 1 to 2 hours before, or intravenously 15 minutes before,induction of anaesthesia or intravenously at the end of anaesthesia.

(Balfour and Goa,1997)

6- It has anxiolytic and/or antipsychotic effect (Balfour and Goa.1997).

6. Dosage and Administration:

	Intravenous dose	Oral dose
Chemotherapy-induced nausea and vomiting CINV	100 mg 30 minutes before chemotherapy	200 mg 1 hour before chemotherapy
Post-operative nausea and vomiting	12.5 mg__200mg	25mg__200mg
Radiotherapy-induced nausea and vomiting RINV	40 mg	0.3 mg/kg

Table 8. dosage and administration of dolasetron

7. Adverse effect:

CNS: 1. headache: the most frequent adverse event. (Diemunsh et al,1995)
2.dizziness. (Dempsey et al,1996)
3.drowsiness. (Dempsey et al,1996)

GIT: 1. hunger. (Lerman et al,1996)
2. constipation (Lerman et al,1996)
3. diarrhea (Rubenstein et al,1997)
4. nausea and abdominal pain
5. hepatic function: elevation in aspartate aminotransferase (AST) and alamine aminotransferase(ALT) after oral treatment which returned to normal on resting 28 days later (Stubbs et al,1997).

CVS:

1. prolongation of the mean PR,QRS and QT_C intervals.
2. premature atrial contraction.
3. bradycardia
4. first degree atrioventricular block (Dempsey et al, 1996)
5. hypotension (Hesketh et al, 1996)
6. tachycardia (Rubenstein et al, 1997)

Adverse Events	All Patients (%) (N – 75)	One-Dose Regimen (%) (n = 37)	Two-Dose Regimen (%) (n = 38)
Headache	13	11	16
Dizziness	5	5	5
Abdominal cramps	4	3	5
Diarrhea	4	3	5
Difficulty Sleeping	4	5	3

8. Contraindication:

1) The drug is contraindicated in patients with pre-existing prolongation of cardiac conduction intervals particularly QTc. (Balfour and Goa, 1997)

That maybe due to cardiac disease e.g.:

- Congestive heart failure
- Cardiomyopathy
- First degree heart block
- Pre-existing complete bundle branch block
- Atrio-ventricular block II to III (Rubenstein et al, 1997)
- Arrhythmia (those receiving class I or III antiarrhythmic agents)

- Cardiotoxicity due to cumulative doses of anthracyclines or anthracenediones. (Audhuy et al, 1996)

2) Abnormal serum potassium or calcium concentration.
3) Significant liver disease (Audhuy et al, 1996)
4) Neurological or psychiatric disease excluding alcoholism. (Fauser et al, 1996)

9. Drug interaction:

1) The efficacy if dolasetron is increased if given concomitantly with corticosteroids. (Balfour and Goa, 1997).
2) Combining dolasetron with dexamethasone has led to an improvement in antiemetic control compared with intravenous dolasetron alone. (Kris et al,1997)

3) Combining dolasetron with drugs that prolong ECG intervals e.g. antiarrhythmic drugs can increase the risk of arrhythmia. (Audhuy et al, 1996)

4) Drugs that inhibit the P_450 enzymes e.g. (cimitedine) can increase hydrodolasetron level. (Fawcett, 1999)

5) Drugs that induce the p_450 enzymes e.g. (rifampin) may reduce hydrodolasetron level (Fawcett, 1999)

10. Special consideration:

- There is no significance difference of the dose with respect to gender, age, height, weight, type of surgery, duration of anesthesia (Diemunsh et al, 1995) this is because all efficacy studies have been conducted with single dose of the drug. Although male sex (Fauser et al, 1996) age > 65 years (Rubenstein et al, 1997), a history of heavy alcohol use (Hesketh et al, 1996) and no previous chemotherapy are significant predictors of good response (Balfour and Goa, 1997).

- The pharmacokinetics of dolasetron and its active metabolitesis influenced by hepatic impairment but not to a clinically important extent (Stubbs et al, 1997).

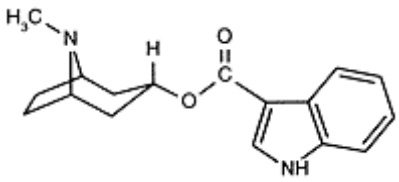
- Use in children:

Intravenous doses of dolasetron ranging from 0.6 to 2.4 mg/kg in children undergo moderately or highly emetogenic chemotherapy (Stubbs et al, 1997).

TROPISETRON

Unlike the other 5- HT3 antagonist, ondansetron (a corbazole) and granisetron (an in dazole), tropisetron is an indole compound. [lee, Plosker and McTavish. 1993]. It has high affinity and specificity for 5- HT3 receptors and antagonized the effects of 5-HT in several tests. In addition, tropisetron appears to have a weak antagonistic effect on 5-HT4 receptors [Roila etal.1997]. Its clinical efficacy in reducing nausea and vomiting depends mainly on the blockage of 5- HT3 receptors.

1. Chemical structure:-



Tropisetron

[Kutz . 1993] [de Bruiji. 1992] [lee etal ,1993]

2. Physical properities:

Tropisetron hydrochlorid is I (alpha) H, 5H-tropan -3- yl indole -3- carboxylate hydrochloride.

Tropisetron hydrochloride is a white of off – white crystalline powder. It is soluble > 5% in water, 1.6% in ethanol and poorly soluble (0.02%) in aceton. The molecular weight of the free base is 284.4 and of the hydrochloride salt are 320.8. [Simpson, 2000].

3. Mechanism of action:

The mechanism of action of 5- HT3 receptor antagonist in blocking radiation and cancer chemotherapy-induce nausea and vomiting is not fully understood. It is possible that cancer chemotherapeutic agents and radiation causes cellular damage to the intestinal mucosa, eliciting the release of serotinin from enterochromoffin cells [Andrews and Bhandari 1993]. Serotonin probably activates vagal and splanchnic efferent neurons so initiating the vomiting reflex. Enterochromaffin cell also have 5- HT3 receptor site that form part of a Positive feedback loop that initials further increases in 5- HT release [Simpson etal, 2000]. A role for serotonin in chemotherapy- induced nausea and vomiting is supported by evidence showing greatly increased plasma levels of serotonin in some patients receiving cisplatin chemotherapy for testicular cancers [Bornes. etal. 1990] In addition, increased plasma level and urinary excretion of 5-hydroxyindole acetic acid, the main metabolite of serotnin, occurred in patients receiving high- dose cisplatin or dacabazine chemotherapy, with the increased paralleling the episodes of emesis [Cubeddu et al . 1992]. 5-HT3 binding sites are present in both the peripheral and central nervous systems and mechanism of action of tropisetron and other 5-HT3 receptor antagonist in preventing nausea and vomiting induced by cancer chenmotherapy and radiation is likely to involve antagonism of the action of serotonin at both these site [Andrews and Bhandari, 1993]. 5-HT also induce vomiting by stimulating the chemoreceptor trigger zone (area posterma) and nucleus tractus solitaries. Tropisetron is thought to prevent acute nausea and vomiting by antagonizing 5-HT3 receptors in peripheral and central nervous systems [Perez. 1998]. Delayed nauseas and vomiting may involve mechanisms other than those mediated thought 5-HT3 receptors [lee etal. 1993]. [Gorgony and Eitinger, 1998].

3. Pharmacokinetics :

Tropisetron is rapidly and almost completely absoded (> 95% of a 100 mg dose within 2.2 hours) after oral administration [de Braijn. 1992]. However the drug under goes saturabble (dose – dependent) first pass metabolism : absolute boiavailabilyt was 52% for a 20mg dose and 66% for a 100mg dose in 1 study in volunteers [Fischer et al 1992]. As the drug is lipophilic, it has a large volume of **distribution** [554 and 463 after IV tropisetron 10 mg in extensive and poor metabolisers respectively ptn binding is 59 to 71% [de Bruiji 1992].

Metabolism of tropisetron occurs predominantly in the liver and involves hydroxylation of the index ring; demethylation is negligible Hydroxymetabolites tropisrten are further metabolized to glucouronides and sulphates [de Bruijin 1992] [Fischer et al 1992] No metabolites of tropiseteron are active [Novarctivs pharma AG 1998] As the cytochrome P450 2 D6 enzyme is involve in the metabolism of tropisetron, there are phenotypic population of extensive and poor metabolizers of the drug.

The plasma terminal elimination half- life (t½) was about 8 hours in extensive metabolizers compared with 30 to 40 hours in poor metabolizers [de Bruijn 1992].

Less than 0.5% of an administered dose of tropisetron (20 or 100mg) is **excreted** unchanged in the faeces (in accordance with the almost completed absorption) [Fischer et al. 1992]. Elimination is almost complete after 120 hours; [Fischer et al. 1992] about 80% of the does can be recovered in the urine as either unchanged tropisetron (≈9%) or its metabolites (≈70%). [De-Bruijn.1992] [Simpson etal. 2000] [Gregory and Ettinger.1998] liver cirrhosis and moderate to server nominal impairment recpectively, reduce metabolic and nonrenal clearance of the drug [De-Bruijn 1992]. However, accumulation of tropistron with the recommended treatment regimen is not expected in any patients group and dosage adjustments are not necessary [De -Bruiji 1992]. Hepatitis and fatty liver do not affect the pharmacokinctics of tropisetron [De Bruijn 1992] Although t ½ values were an affected by age in children plasma clearance was lower in Childs aged 3to 6 years than in those aged 10 to 15 years [Gaedicke etal. 1996] volume of distribution was also lower in the younger children and this resulted in a reduction in drug clearance.

Interaction are not expected with drugs that affected protein binding or inhibit the cytochrome P450 system, but inducers of the cylochrom P450 system (e.g: phenytoin) may affect tropisetron pharmacokinetics [de Bruijn. 1992] [lee etal. 1993].

4. Theraputic uses:

1-Management of nausea and vomiting induced by cytotoxic therapy:-

Tropisetron 5mg per drug is an effective and well tolerated antiemetic treatment. It can he administered without special precaution to all patients who undergo aggressive chemotherapy. Tropisetron is effective in preventing nausea and vomiting induced by cytotoxic treatment during multiple chemotherapy course the efficacy of tropisetron compares well with even the best currently available, but complicated, antiemetic cocktails and tropisetron is much better tolerated. The simple dosing schedule of either injection or 1 capsule per day makes tropisetron ideal for both in-patient and out- patients. [De Bruijn. 1992] [lee etal. 1993] [yalcin etal . 1999] [Mystakide etal . 1998] [Malik etal. 1999].

2-Treatment and prevention of post operative nausea and vomiting:

For the treatment of postoperative nausea and vomiting the equivalent of triplication 2 mg may be given by slowly IV injection, or by infusion over 15 minutes, within 2 hours of the end of anesthesia. For prophylactic, the same dose may be given shortly before induction of anesthesia. [Melkkila etal. 1996] [Alan etal. 1998]
[lee etal. 1993] [Jakobsson etal. 1999] [ANG Habre and Sims. 1998] [Zomers etal. 1993].

3 Anxiety disorder:-

A dose – dependent anxiolytic effect was reported for tropisetron when studied in patients with generalized anxiety [Lecrubier. Etal . 1993] but clinical evidence for the benefits 5 HT3 receptors antagonists in anxiety disorder is lacking [Gernshaw and Silverstone . 1997]

5. Pharmacological effects:

- Tropisetron (novaban) is highly potent and selective antegonist of 5-HT3 receptors. (k1 value for 5HT3 recptors of 0.32 to 3.1 normal / L .
- It has no affinity for the 5-HT4 receptor tropisetron acts as a weak 5HT3 receptor antagonist at concentration 1000 times greater than those which exert 5-HT3 receptor antagonist effects (K1 value approximately 1000 n mol / L) [Bhandar, and Andrews. 1991].
- Tropisetron has little or no affinity for 5HT1, 5HT2, dopamine D1 and D2, histamine H1, muscarinic or benzodiazepine receptors, or for α 1, α 2, β1 or β2, advenoceptors. [lee etal. 1993] .
- tropisetron binds to central and peripheral nervous system sites [Simpson etal. 2000]
- topisetron is inactive at the dopmine d1 receptor with a k1 value > 10 000 nmol/L . and therefore tropisetron is unlikely to cause extra pyramidal effects. [lee etal. 1993].
- Intravenously administered tropisetron 1 mg /kg inhibited the reflex bradycardia induced by intravenous administration of sertonin [Von Bezold- Jarisch reflex] such that a 4 - fold increase in the dose of serotonin was required to produce the same reflex reduction in heart rate. [Simpson etal. 2000].
- Tropisetron inhibited the pain caused by serotonin when applied locally to a blister base on the human arm.

- The protein binding of tropisetron is moderate (59 to 71%) ; there fore, no drug- drug interaction due to displacement of the drug from its binding site are to be expected.
- Tropisetron showed no inductive or inhibitory effects on cytochrome P450- dependent enzymes that are not linked to the *11*D6 polymorphism and inhibition of these enzymes had only a minor influence on the pharmacokinetice of tropisetron.
- Here is no evidence on the topisetron at the recommended dose causes ECG or Laboratory abnormalities [suarez etal, 1994].
- No evidence emerged that tropisetron contributed to or exacerbates cisplatine nephrotoxicity or neurotoxicity.
- Dosages higher than recommended 5 mg per day hypertensive episodes occasionally occurred, especially in patients with pre-existing and inadequately controlled hypertension who received 20 to 80 of tropisetron.
- There is no evidence emerged that tropisetron aggravates the risk of bone morrow toxicity resulting from aggressive cisplatin chemotherapy. [sorbe 1993].

6. Adverse effects:

- The most common adverse enents are headache, constipation, diarrhea and fatigue [de Bruijn. 1993]. Adverse events were usually mild and each type event occurred in 8 to 27% of patients more recent noncomparative trial involving a larger number of patients indicate a similar tolerability profile for tropisetron , headache, constipation, fatigue, epigastric pain, dizziness and allergy were most frequently reported, with fever, diarrhoea, erythema and heart symptoms being reported infrequently (< 0.5%) [sorb etal 1994)] [Bleiberg etal, 1998]. Laboratory and ECG

data are generally unaffected by the recommended dosage of tropisetron (Novaitis pharma Ag, 1998)

- Review of more than 80 000 patients treated with tropisetron revealed no reports of marked extrapyramidal effets [Novartis pharma AG, 1198] [simpson etal. 2000] [lee, Plosker and Mc Tavish. 1993].
- Tropisetron may cause hypertention in large dose especially in uncontrolled pre- existing hypertensive patiens [de- Bruijn, 1992]

7. Drug interaction:

The protein binding of tropisetron is moderate (59 to 71%):

Therefore, no drug-drug interactions due to displacement of the drug from its binding site are to be expected. Tropisetron showed no inductive or inhibitory effects on cytochrome P450- dependent enzymes that are not linked to the 11 D6 polymorphism and inhibition of these enzymes had only a minor influence on the pharmcokinetis of tropisetron. In contrast, induction of the cytochrome P450 system shortens the elimination half-life and increases the metabolic clearance of tropisetron. These when tropisetron is administered to extensive metabolism in combination with enzyme- inducing drug such as phenytoin, the dose needs to be increased in order to achieve the same exposure as in subjects not receiving enzyme-inducing agents. [de bruijn , 1992].

- Drugs that probably share the same excretory pathway as tropisetron at the renal tubules, such as cimetidine, may increase the plasma concentration of tropsetron, but not at the 5mg dose level [de Bruijn, 1992].

8. Contraindication and Precaution:

I. Tropisetron is contraindicated in pregnant women and should not be used by those who are breastfeeding [Novartis 1998-99]. [simpson etal. 2000]
II. Tropsetron dosage adjustment is not required in poor metabolisers of the drug although the elimination half-life is prolonged in this population. [Simpson etal. 2000]
III. No adjustment of the 6-day recommended course of tropisetron is required in patients with hepatic or renal impairment or elderly patients [Simpson etal. 2000]
IV. The recommended dosage should not be exceeded in patients with uncontrolled hypertension [Simpson, Spencer and McClellan, 2000].
V. The dosage of tropisetron may need to be increased in extensive metabolisers of the drug who are also taking liver enzyme- inducing drug such as rifampicin or Phenobarbital [Novartis, 1998-99] [Simpson etal. 2000]

9. Dosage and administration:

Tropisetron is available as 5mg capsules for oral administration and in ampoules containing 5mg (or 2mg) of tropisetron here for oral or intravenous use, the contents of an ampoule can be mixed juice or soft drink and given to children drink. [Novartis 1998-99] [Simpson etal. 2000]. The recommended dosage for oral and intravenous administration is 5mg daily for 6 days adults and 0.2mg/kg up to a maximum of 5mg for children aged >2 years. It is recommended to give tropisetron intravenously shortly

before chemotherapy on day 1, either as an infusion or as a slow (<1 minute) injection, and subsequenthy orally each morning. 1 hour before food [Novartis , 1998-99]. Oral agents are as effective and well tolerated as IV antiemetic and are generally less costly and more convenient [Grall etal 1999] [simpson etal. 2000].

VI. CONCLUSION

The 5-HT3 receptor antagonists are highly effective antiemetic drug that when used in combination with dexamethasone represents the most efficacious regimens for the prevention of acute emesis induced by cisplatin and by moderately emetogenic chemotherapy. Pre-clinical differences among 5-HT3 receptor antagonists have been shown and this has stimulated many comparative clinical studies at present, large randomized, double-blind studies have clearly shown that the anti-emetic efficacy and tolerability of ondansetron, granisetron, tropisetron and dolasetron are almost identical in the prevention of cisplatin-induced emesis. Therefore in this case the choices among the 5-HT3 receptor antagonist, should be based the cost, acquisition costs of 5-HT3 antagonists can very considerably, making the most financially attractive choice for one institution different from that of another the rout of administration and the total daily dose used must be considered when examining cost. Using lower doses of antiemetics to lower cost of therapy must be balance against the likelihood of failing to prevent nausea and vomiting. The decision as to which antiemetic is most cost effective can only be made once the optimal dose and schedule for the given drug in the target population is established.

There are, at present, no major differences in the tolerability of the various 5-HT3 receptors antagonist, but more data are needed from the monitoring systems of various countries.

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