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SHORT REVIEW ON DOMPERIDONE TABLET

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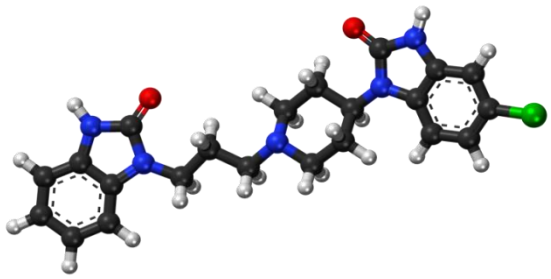
ABSTRACT

Oral route is presently the gold standard in the pharmaceutical industry where it is regarded as the safest, most economical and most convenient method of drug delivery resulting in highest patient compliance. Pediatric and geriatric patients find it difficult to swallow solid dosage forms like tablets. Mouth dissolving tablet that dissolve or disintegrate rapidly in oral cavity result in solution, is an ultimate remedy for this problem in addition they give pleasing mouth feeling. ODT has advantages such as patient compliance, quick onset of action, improved bioavailability. Domperidone tablet (ODT) gives relief from nausea, vomiting. This review gives us all information about pharmacokinetic, pharmacodynamic, uses, precautions, side effects of domperidone tablets

INTRODUCTION

It is a drug developed by Janssen Pharmaceutical that acts as a peripherally selective antagonist of the dopamine D_2 and D_3 receptors. It is administered orally, rectally, or intravenously. Domperidone is used to relieve nausea and vomiting; to increase the transit of food through the stomach (that is, as a prokinetic agent via increasing gastrointestinal peristalsis); and to promote lactation (breast milk production) by release of prolactin. It is also used in scientific research to study the biological function of dopamine, an important neurotransmitter and hormone, in the body. Domperidone is available in the form of tablets, orally disintegrating tablets suspension and suppositories.

STRUCTURE OF DOMPERIDONE



[1]

MECHANISM OF ACTION

Domperidone is a peripheral dopamine D_2 and D_3 receptor antagonist. It provides relief from nausea by blocking receptors at the chemoreceptor trigger zone (a location in the nervous system that mediates nausea) at the floor of the fourth ventricle (a location near the brain). It increases motility in the upper gastrointestinal tract to a moderate degree and increase lower esophageal sphincter pressure by blocking dopamine receptors the gastric antrum and the duodenum. It blocks dopamine receptors in the anterior pituitary gland increasing release of prolactin which in turn increases lactation. Domperidone may be more useful in some patients and cause harm ino thers by way of the genetics of the person, such as polymorphisms in the drug transporter gene ABCB1 (which encodes P-glycoprotein), voltage-gated potassium channelhERG/Kv11.1 and the α1D—adrenoceptor[2]

Dopamine receptors are G protein-coupled receptors that are prominent in the vertebrate central nervous system (CNS). Dopamine receptors are implicated in many neurological processes, including motivation, pleasure, cognition, memory, learning, and fine motor control, as well as modulation

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of neuroendocrine signaling. Abnormal dopamine receptor signaling and dopaminergic nerve function is implicated in several neuropsychiatric disorders [1]. Thus, dopamine receptors are common neurologic drug targets; antipsychotics are often dopamine receptor antagonists while psychostimulants are typically indirect agonists of dopamine receptors.[3]

Domperidone Tablet: Pharmacodynamics

Domperidone tablet is a peripherally selective dopamine D_2 and D_3 receptor antagonist. It has no clinically significant interaction with the D_1 receptor, unlike metoclopramide. The drug provides relief from nausea by blocking receptors at the chemoreceptor trigger zone (a location in the nervous system that mediates nausea) at the floor of the fourth ventricle (a location near the brain). It increases motility in the upper gastrointestinal tract to a moderate degree and increases lower esophageal sphincter pressure by blocking dopamine receptors in the gastric antrum and the duodenum. It blocks dopamine receptors in the anterior pituitary gland increasing release of prolactin which in turn increases lactation. [4]

Effects on prolactin levels

A single 20 mg oral dose of domperidone has been found to increase mean serum prolactin levels (measured 90 minutes post-administration) in non-lactating women from 8.1 ng/mL to 110.9 ng/mL (a 13.7-fold increase).This was similar to the increase in prolactin levels produced by a single 20 mg oral dose of metoclopramide (7.4 ng/mL to 124.1 ng/mL; 16.7-fold increase).After two weeks of chronic administration (30 mg/day in both cases), the increase in prolactin levels produced by domperidone was reduced (53.2 ng/mL; 6.6-fold above baseline), but the increase in prolactin levels produced by metoclopramide, conversely, was heightened (179.6 ng/mL; 24.3-fold above baseline).

This indicates that acute and chronic administration of both domperidone and metoclopramide is effective in increasing prolactin levels, but that there are differential effects on the secretion of prolactin with chronic treatment.The mechanism of the difference is unknown.The increase in prolactin levels observed with the two drugs was, as expected, much greater in women than in men. This appears to be due to the higher estrogen levels in women, as estrogen stimulates prolactin secretion.

For comparison, normal prolactin levels in women are less than 20 ng/mL, prolactin levels peak at 100 to 300 ng/mL at parturition in pregnant women, and in lactating women, prolactin levels have been found to be 90 ng/mL at 10 days postpartum and 44 ng/mL at 180 days postpartum[5]

Effects on TSH levels

Along with prolactin, domperidone has, to a lesser extent, been found to increase the secretion of thyroid-stimulating hormone (TSH), even in patients with hypothyroidism. A single 4 mg intravenous dose of domperidone produced peak TSH levels of 1.9-fold above baseline and peak prolactin levels of 23-fold above baseline (which occurred at 30 minutes post-administration) in women with hypothyroidism.Levels of TSH and prolactin decreased to 1.6-fold and 17-fold above baseline, respectively, at 120 minutes post-administration[6]

Domperidone Tablet: Pharmacokinetic Properties

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hr after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide

tissue distribution, but low brain concentration. Small amount of drug crosses the placenta in rats.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency. With oral administration, domperidone is extensively metabolized in the liver (almost exclusively by CYP3A4/5, though minor contributions by CYP1A2, CYP2D6, and CYP2C8 have also been reported)and in the intestines.[5] Due to the marked first-pass effect via this route, the oral bioavailability of domperidone is low (13–17%); conversely, its bioavailability is high via intramuscular injection (90%). The terminal half-life of domperidone is 7.5 hours in healthy individuals, but can be prolonged to 20 hours in people with severe renal dysfunction.All of the metabolites of domperidone are inactive as D_2 receptor ligands.The drug is a substrate for the P-glycoprotein (ABCB1) transporter, and animal studies suggest that this is the reason for the low central nervous system penetration of domperidone.[7]

Domperidone Tablet: Uses

The uses or *indications* of domperidone vary between nations. For instance, in Italy it is used in the treatment of gastroesophageal reflux disease and in Canada, the drug is indicated in upper gastrointestinal motility disorders and to prevent gastrointestinal symptoms associated with the use of dopamine agonist antiparkinsonian agents. In the United States, domperidone is not currently a legally marketed human drug and it is not approved for sale in the U.S. On June 7, 2004, FDA issued a public warning that distributing any domperidone-containing products is illegal. In the United Kingdom, domperidone is only indicated for the treatment of nausea and vomiting and the treatment duration is usually limited to 1 week.Nausea and vomitingThere is some evidence that domperidone has antiemetic activity. It is recommended in the Canadian Headache Society's guidelines for treatment of nausea associated with acute migraine.

a. Gastroparesis

It is a medical condition characterised by delayed emptying of the stomach when there is no mechanical gastric outlet obstruction. Its cause is most commonly idiopathic, a diabetic complication or a result of abdominal surgery. The condition causes nausea, vomiting, fullness after eating, early satiety (feeling full before the meal is finished), abdominal pain and bloating.Domperidone may be useful in diabetic and idiopathic gastroparesis.However, increased rate of gastric emptying induced by drugs like domperidone does not always correlate (equate) well with relief of symptoms.[8]

b. Parkinson's disease

Parkinson's disease is a chronic neurological condition where a decrease in dopamine in the brain leads to rigidity (stiffness of movement), tremor and other symptoms and signs. Poor gastrointestinal function, nausea and vomiting is a major problem for people with Parkinson's disease because most medications used to treat Parkinson's disease are given by mouth. These medications, such as levodopa can cause nausea as a side effect.

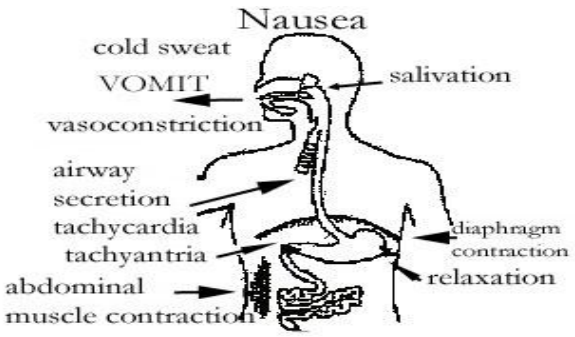
Furthermore, anti-nausea drugs, such as metoclopramide, which do cross the blood–brain barrier may worsen the extra-pyramidal symptoms of Parkinson's disease.Domperidone can be used to relieve gastrointestinal symptoms in Parkinson's disease, because, even though it blocks dopamine receptors (which would be expected to worsen Parkinson's disease), it does not cross the blood–brain barrier (the barrier between the blood circulation of the brain and the rest of the body). In addition to this, domperidone may enhance the bioavailability (effect) of levodopa (one of the main treatments in Parkinson's disease).

Although these features make domperidone a useful drug in Parkinson's disease, caution is needed due to the cardiotoxic side effects of domperidone especially when given intravenously, in elderly people and in high doses (> 30 mg per

day). A clinical sign of domperidone's potential toxicity to the heart is the prolongation (lengthening) of the QT interval (a segment of the heart's electrical pattern).Functional dyspepsiaDomperidone may be used in functional dyspepsia in both adults and children.[9]

c. Nausea and vomiting

There is some evidence that domperidone has antiemetic activity. It is recommended in the Canadian Headache Society's guidelines for treatment of nausea associated with acute migraine.



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Domperidone Tablet: Side effects

a. Penetration of immature blood brain barrier

In Britain a legal case involved the death of two children of a mother whose three children had all had hypernatraemia. She was charged with poisoning the children with salt. One of the children, who was born at 28 weeks gestation with respiratory complications and had a fundoplication for gastroesophageal reflux and failure to thrive was prescribed domperidone An advocate for the mother suggested the child may have suffered neuroleptic malignant syndrome . as a side effect of domperidone due to the drug crossing the child's immature blood brain barrier.[11]

b. Cardiac side effects

UK drug regulatory authorities (MHRA) have issued the following restriction on domperidone due to increased risk of adverse cardiac effects. "Domperidone (Motilium) is associated with a small increased risk of serious cardiac side effects. Its use is now restricted to the relief of nausea and vomiting and the dosage and duration of use have been reduced. It should no longer be used for the treatment of bloating and heartburn. Domperidone is now contraindicated in those with underlying cardiac conditions and other risk factors. Patients with these conditions and patients receiving long-term treatment with domperidone should be reassessed at a routine appointment, in light of the new advice".

c.Other side effects

Due to D_2 receptor blockade, domperidone causes hyperprolactinemia. Hyperprolactinemia can suppress the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, in turn suppressing the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and resulting in hypogonadism (low sex hormone (e.g., testosterone, estradiol) levels).As such, male patients may experience low libido, erectile dysfunction [12]

DOMPERIDON SCHEDULE H DRUG

Schedule H is a class of prescription drugs in India appearing as an appendix to the Drugs and Cosmetics Rules, 1945 introduced in 1945. These are drugs which cannot be purchased over the counter without the prescription of a qualified doctor. The manufacture and sale of all drugs are covered under the Drugs and Cosmetics Act and Rules. It is revised at times based on the advice of the Drugs Technical Advisory Board, part of the Central Drugs Standard Control Organization in the Ministry of Health and Family Welfare domperidone is used to relieve feelings of sickness (nausea) or being sick (vomiting). Feeling sick can be a common symptom, but it may be due to a number of different causes. You will only be recommended an anti-emetic like domperidone if the cause of your sickness is known.Domperidone works by helping to move the food in your stomach through your digestive system more quickly. This helps to stop you from feeling sick. [13]

DOMPERIDONE Tablet: Dose

Domperidone is an anti-emetic which can stop you feeling sick. Each tablet contains 10mg domperidone as domperidone maleate. Domperidone is used to treat: nausea and vomiting complaints of the stomach, which occur with delayed emptying of the stomach. This can result in symptoms such as feeling full (during or just after eating), bloating, belching, nausea, heartburn and stomach ache. These tablets have been prescribed for you by a doctor. Take them exactly as he or she has told you. Please read the label carefully. Domperidone should be used at the lowest effective dose in adults and children. The tablets should be swallowed whole with a sufficient quantity of liquid (e.g. one glass of water).

Adults and adolescents

The usual dose for the treatment is 1 to 2 tablets taken 3 to 4 times a day before meals. Do not take more than 8 tablets (80mg) in 24 hours.

Infants and Children

Weighing less than 35kg (5 stone) should not take these tablets. The usual dose for the treatment is 0.25 0.5mg per kg bodyweight taken 3 to 4 times a day before meals. Your pharmacist may be able to help you if you are not sure.

People with kidney problems

Your doctor may tell you to take a lower dose or take the medicine less often. Your doctor may advise you to take your medicine in a different way, so you should always follow your doctor s advice about how and when to take your medicine and always read the label. If you feel that the effect of Domperidone 10mg Tablets is too strong or too weak, talk to your doctor or pharmacist. If your complaint shows no improvement after 28 days while taking Domperidone 10mg Tablets, consult your doctor to see if you need to go on taking this medicine. [14]

PRECAUTIONS

Like all medicines, Domperidone 10mg Tablets can have sideeffects Tell your doctor your medical history, especially of: history of breast cancer, allergies. Limit your intake of alcoholic beverages. This medication should be used only if clearly needed during pregnancy. Discuss the risks and benefits with your doctor. Domperidone passes into breast milk.

DRUG INTERACTIONS

Because this medication enhances movement in the digestive tract, it may affect the absorption and action of other medications. Therefore, it is important to tell your doctor of any nonprescription or prescription medication you may take, especially of: MAOIs (e.g., furazolidone, phenelzine, selegiline, tranylcypromine). Do not start or stop any medicine without doctor or pharmacist approval.

OVERDOSE

If overdose is suspected, contact your local poison control center or emergency room immediately. US residents can call the US national poison hotline at 1-800-222-1222. Canadian residents should call their local poison control center directly. Symptoms of overdose may include drowsiness, dizziness, confusion, twitching, muscle rigidity, and irregular heartbeat. [15]

CONCLUSION

This review gives us all detailed knowledge about Domperidone tablet and concludes that it is considered better as an antiemetic in children.

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