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Domperidone: Mechanism of Action and Clinical Uses

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Abstract

Domperidone is a dopamine receptor antagonist that exerts its effects primarily in the gastrointestinal tract. It is widely used to manage gastrointestinal motility disorders such as gastroparesis and nausea associated with various conditions, including chemotherapy and Parkinson's disease. This comprehensive review explores the mechanism of action of domperidone, its pharmacokinetics, clinical uses across different patient populations, efficacy, safety profile, and current controversies surrounding its use.

Keywords: Domperidone • Gastroparesis • Nausea

Introduction

Domperidone, chemically known as 5-chloro-1-(1-[3-(2-oxo-2, 3-dihydro-1H-benzimidazol-1-yl) propyl] piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one, belongs to the class of dopamine receptor antagonists. Unlike other drugs in its class, domperidone exhibits peripheral selectivity, primarily targeting dopamine D_2 and D_3 receptors in the gastrointestinal tract without significant central nervous system penetration due to its poor blood-brain barrier permeability. Domperidone acts by antagonizing dopamine receptors, particularly D2 and D3 receptors, in the Chemoreceptor Trigger Zone (CRTZ) and the gastrointestinal tract. By blocking these receptors, domperidone increases the release of acetylcholine from enteric neurons, thereby enhancing gastrointestinal motility and promoting gastric emptying. This prokinetic effect is beneficial in conditions characterized by delayed gastric emptying, such as gastroparesis, and in alleviating symptoms of nausea and vomiting. Following oral administration, domperidone is rapidly absorbed from the gastrointestinal tract. However, its bioavailability is variable due to extensive first-pass metabolism in the liver, primarily mediated by Cytochrome P450 enzymes (CYP3A4). Peak plasma concentrations are reached within 30 to 60 minutes, and the drug undergoes significant enterohepatic circulation. Domperidone is predominantly eliminated via the hepatic route, with a half-life ranging from 7 to 9 hours in healthy individuals [1].

Literature Review

Domperidone is widely prescribed for the management of gastroparesis, a condition characterized by delayed gastric emptying often associated with diabetes mellitus or idiopathic causes. By enhancing gastrointestinal motility, domperidone helps alleviate symptoms such as nausea, early satiety, and postprandial fullness, thereby improving overall quality of life for patients with gastroparesis. In addition to gastroparesis, domperidone is effective in controlling nausea and vomiting induced by various factors, including chemotherapy, radiotherapy, and postoperative recovery. Its peripheral action and minimal central nervous system penetration make it a preferred choice in managing nausea without causing sedation or extrapyramidal symptoms commonly associated with centrally acting dopamine receptor antagonists [2].

Domperidone has also gained attention for its off-label use in stimulating lactation. By increasing prolactin secretion via dopamine receptor blockade, domperidone can enhance milk production in lactating women experiencing insufficient milk supply. This application has led to its use in promoting breastfeeding success, although regulatory agencies emphasize cautious prescribing due to potential cardiac risks. Clinical studies have demonstrated the efficacy of domperidone in improving symptoms of gastrointestinal motility disorders and nausea. However, concerns about its cardiovascular safety, particularly the risk of QT interval prolongation and ventricular arrhythmias, have prompted regulatory agencies to restrict its use and recommend careful monitoring, especially in patients with underlying cardiac conditions or those taking concomitant medications known to prolong QT interval [3].

Discussion

The use of domperidone has been subject to regulatory scrutiny and controversy, particularly concerning its cardiac safety profile. Regulatory agencies in various countries have issued warnings and guidelines to mitigate the risk of cardiac adverse effects. European Medicines Agency (EMA) has recommended restrictions on the use of domperidone, advising lower doses and shorter treatment durations to minimize cardiac risks. U.S. Food and Drug Administration (FDA), Domperidone is not approved for use in the United States. The FDA has issued warnings regarding its potential cardiac risks, particularly when used for enhancing lactation [4].

Domperidone's metabolism via CYP3A4 makes it susceptible to interactions with other drugs that inhibit or induce this enzyme. CYP3A4 Inhibitors, concomitant use with potent CYP3A4 inhibitors such as ketoconazole, erythromycin and ritonavir can increase domperidone levels, raising the risk of adverse effects, particularly cardiac arrhythmias. QT-Prolonging Drugs, combining domperidone with other medications that prolong the QT interval should be avoided to minimize the risk of serious cardiac events. Despite its clinical benefits, domperidone remains a subject of controversy due to safety concerns, particularly regarding its cardiac effects. Regulatory agencies in various countries have implemented restrictions on its use, emphasizing the need for risk stratification and patient monitoring. Ongoing research focuses on identifying safer alternatives or refining dosing strategies to mitigate these risks while maximizing therapeutic efficacy [5].

Ongoing research aims to further clarify the safety profile of domperidone and explore new therapeutic applications. Studies are being conducted to better understand the mechanisms behind domperidone-induced cardiac arrhythmias and to identify patient populations at higher risk. Researchers are investigating other prokinetic agents with potentially safer profiles to provide alternatives to domperidone for gastrointestinal motility disorders. Further studies are needed to evaluate the long-term safety and efficacy of

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domperidone for lactation enhancement, particularly in breastfeeding women with underlying health conditions [6].

Conclusion

Domperidone is a valuable medication in the management of gastrointestinal motility disorders and nausea, offering peripheral dopamine receptor antagonism without significant central nervous system effects. Its mechanism of action, pharmacokinetics, clinical uses, efficacy, and safety profile make it a versatile option in clinical practice. However, clinicians must weigh its benefits against potential risks, particularly cardiovascular concerns, and adhere to regulatory guidelines to ensure safe and appropriate use.

Acknowledgement

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Conflict of Interest

None.

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