World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 6, Issue 12, 2017 ISSN: 2319-5622 USA CODEN: JPROK3

Review Article

RECENT UPDATE ON METOCLOPRAMIDE: A REVIEW

Swati Mishra *, Neelesh Choubey, Harish Pandey and Himesh Soni

College of Pharmacy, SSSUTMS, Sehore (M.P.) - 466001, INDIA.

Received on: 05-12-2017; Revised and Accepted on: 23-12-2017

ABSTRACT

Metoclopramide's(methoxy-2-chloro-5 -procainamide) effect on the medullary chemoreceptor trigger zone makes it useful as a routine anti-emetic and in preventing vomiting induced by antineoplastic drugs, particularly cisplatin. Metoclopramide's gastrointestinal smooth muscle stimulatory effects are related to its ability to antagonize the inhibitory neurotransmitter, dopamine, to augment acetylcholine release and sensitize the muscarinic receptors of the gastrointestinal smooth muscle; and to coordinate gastric-pyloric-small intestinal motor function. In present review attempt had been made to covers all the aspect of works done on drug Metoclopramide including their pharmacological effect, pharmacokinetic parameters and work on analytical methods available for their determinations.

KEYWORDS: *Metoclopramide, Anti-Emetic, Recent Update.*

INTRODUCTION

Metoclopramide (methoxy-2-chloro-5 -procainamide) has been studied in this country for 8 years. Metoclopramide hydrochloride a derivative of para-amino-benzoic acid, is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux [1] and for the prevention of cancer chemotherapy- induced emesis [2]. Metoclopramide is a medication used mostly for stomach and esophagealproblems. It is commonly used to treat and prevent nausea and vomiting, to help with emptying of the stomach in people with delayed stomach emptying, and to help with gastroesophageal reflux disease. It is also used to treat migraine headaches [3-4].

Histroy: Metoclopramide was first described by Louis Justin-Besançon and Charles Laville in 1964, while working to improve the anti-dysrhythmic properties of procainamide. That research project also produced the product sulpiride. The first clinical trials were published by Tourneu et al. in 1964 and by Boisson and Albot in 1966. Justin-Besançon and Laville worked for Laboratoires Delagrange[and that company introduced the drug as Primperan in 1964. Laboratoires Delagrange was acquired by Synthelabo in 1991 which eventually became part of Sanofi. A.H. Robins introduced the drug in the US under the tradename Reglan in 1979 as an injectable and an oral form was approved in 1980. in 1989 A.H. Robins was acquired by American Home Products, which changed its name to Wyeth in 2002. The drugs were initially used to control nausea for people with severe headaches or migraines, and later uses for nausea caused by radiation therapy and chemotherapy, and later yet for treating nausea caused by anesthesia. In the US the injectable form was labelled for chemotherapy-induced nausea and the oral form was eventually labelled for gastroesophageal reflux disease. It became widely used in the 1980s, becoming the most commonly used drug to treat anesthesia-induced nausea and for treating gastritis in emergency rooms. The first generics were introduced in 1985 [5-10].

***Corresponding author:**

Swati Mishra

College of Pharmacy,

SSSUTMS, Sehore (M.P.) - 466001, INDIA.

** E-Mail: himeshsoni@rediffmail.com*

DOI: https://doi.org/10.5281/zenodo.1135341

Pharmacological Action:

Metoclopramide is a new generation of dopamine antagonist first described by Justin-Bescanon and associates [11] in the early 1960's, 10 years after the synthesis of procainamide. Both drugs are derived from substituted benzene compounds with para-aminobenzoic acid as the parent compound. The two drugs differ in that procainamide lacks the 5-chloro and 2-methoxy aryl substituents. However, there is a great difference in their pharmacodynamics in that metoclopramide effects the gastrointestinal smooth muscle, as well as being a powerful centrally acting anti-emetic; procainamide is a well-known local anesthetic with recently appreciated anti-arrythmic properties [12].

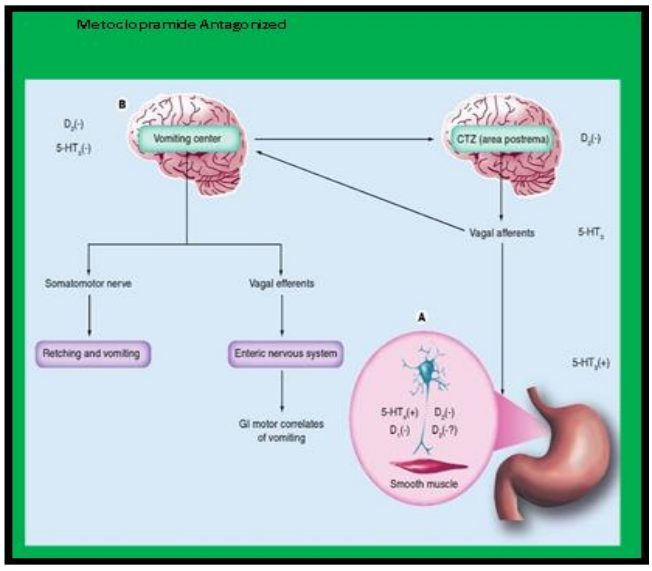

Fig. 1: Pharmacological Action of Metoclopramide

Chemistry:

Metoclopramide is a substituted benzamide and a derivative of para-aminobenzoic acid (PABA) that is structurally related to procainamide, with gastroprokinetic and antiemetic effects. Metoclopramide exerts its prokinetic effect by antagonizing dopamine mediated relaxation effect on gastrointestinal smooth muscle. This enhances the response of the gastrointestinal smooth muscle to cholinergic stimulation, thereby leading to an increase of gastric emptying into the intestines. Metoclopramide may also strengthen the lower esophagus sphincter, thereby preventing acid reflux. This agent antagonizes D2 dopamine receptors in chemoreceptive trigger zone (CTZ) of the medulla, thereby preventing nausea and vomiting [13].

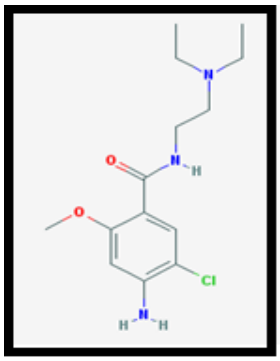

Fig. 2: Structure of metoclopramide

Pharmacokinetic:

Metoclopramide is rapidly and well absorbed from the gastrointestinal tract, and in man undergoes variable first-pass metabolism (oral bioavailability 32 to 100%). In man, N-4 sulphate conjugation is an important pathway of metabolism and after oral administration the ratio of free to conjugated metoclopramide in urine correlates with the plasma AUC. The elimination half-life of metoclopramide is dose-dependent after both intravenous and oral administration of single doses between 5 and 20mg. Metabolic profiles in animal species studied are very different from man. The clearance of metoclopramide is reduced in patients with renal failure to approximately 50% of normals and the terminal half-life is prolonged; this is despite the fact that renal clearance of free drug accounts for only 20% of the administered dose in normals. Absorption: Well absorbed from the GI tract, from rectal mucosa, and from IM sites. Distribution: Widely distributed into body tissues and fluids. Crosses blood-brain barrier and placenta. Enters breast milk in concentrations greater than plasma. Metabolism and Excretion: Partially metabolized by the liver; 25% eliminated unchanged in the urine. Half-life: 2.5– 6 hr [14].

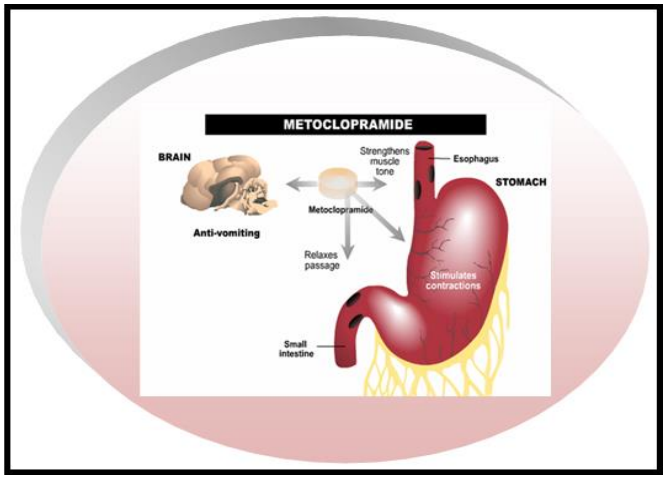

Fig. 3: Thereupatic uses

Estimation of Metoclopramide hydrochloride by various analytical Techniques:

Dudhane N.P et al 2010 developed a simple, specific, accurate, precise and reproducible method has been developed and validated for the simultaneous estimation of metoclopramide hydrochloride and paracetamol in combined dosage form by UV Spectrophotometric method. UV Spectrophotometric method includes Simultaneous Equation method (Method I), Absorbance Ratio method (Method II) and correction method (Method III), For development of Method I, wavelengths selected were 243.0 nm and 273.5 nm for estimation of metoclopramide hydrochloride (MET) and paracetamol (PAR) respectively while for Method II, 243.0 nm λmax for paracetamol, 262.0 nm Isoabsorptive point of Par and Met and 309.0 nm for correction method. The two drugs follow Beer-Lambert's law over the concentration range of 4-16 µg/mL for MET and 4-16 µg/mL for PAR. The % estimation of the drugs was found near to 100 % representing the accuracy of the three methods. The recovery of the MET and PAR were found near to 100 %. Validation of the proposed methods was carried out for its accuracy, precision, specificity and ruggedness according to ICH guidelines. The proposed methods can be successfully applied in routine work for the determination of metoclopramide hydrochloride and paracetamol in combined dosage form [15].

Ahmad Khan et al 2012 developed sensitive and cost effective reverse phase high performance liquid chromatographic method for the estimation of Metoclopramide Hydrochloride in oral solid dosage formulations. A reverse chromatographic method was used with the mobile phase of Acetonitrile, 20m M Potassium dihydrogen phosphate buffer solution (pH 3 adjusted with orthophosphoric acid) in the ratio of 40:60. The column used was Waters C18 3.9×300mm µBondapak (RP). The flow rate of the mobile phase was 2ml/minute. The detector was set at the wavelength of 275nm.This method showed good sensitivity. The linearity was also found to be excellent (γ2=0.997) in the range of 5-75 µg/ml. No interfering peaks were observed at the retention time of Metoclopramide Hydrochloride when both placebo and blank samples were injected (Retention time =1.93min). The parameters such as specificity, linearity, range, accuracy, precision, system suitability, solution stability, detection and quantification limits were evaluated to validate this method. This method can effectively be used for quantitative analysis of Metoclopramide hydrochloride tablet formulations because of its specificity, accuracy and convenience of use(16).

Various studied done on Metoclopramide:

Randale SA et al., 2010 masked the intensely bitter taste of metoclopramide and formulated rapid disintegrating tablets of the taste masked drug. Taste masking was done by complexing metoclopramide with Eudragit in different ratio by the extrusionprecipitation method. Drug-polymer complexes (DPCs) were tested for drug content, in vitro taste in simulated salivary fluid, taste evaluation in oral cavity. The complex having drug-polymer ratio of 1 : 2 shows significant taste masking, confirmed by drug. Prepared tablets were evaluated for various parameters like tensile strength, wetting time, water absorption ratio, in vitro disintegration time and disintegration in oral cavity [17].

Goel H et al., 2010 developed a disintegrating system that could be used for preparing fast disintegrating tablets of highly water soluble drug metoclopramide without compromising on the mechanical strength. For this purpose disintegrating system consisting of chitosan-alginate (CTN-ALG) complex (1:1): glycine and chitin was developed. The results revealed that when CTN-ALG and glycine were mixed in the ratio of 30:70, the granules exhibited a minimum water sorption time and maximum effective pore radius. The results suggested incorporation of chitin (5-10%w/w) while preparing FDTs of metoclopramide to enhanced the disintegration without compromising their mechanical strength [18].

Dahima R and Sharma R, 2010 masked the intensely bitter taste of metoclopramide hydrochloride and to formulate orodispersible tablets of taste mask drug. Drug-resin complex were optimize by considering parameters such as optimization of resin concentration, optimization of swelling time, optimization of stirring time, optimization of pH and optimization of temperature on maximum drug loading. *In vitro* drug release study of taste masked tablets showed that more than 85% of the

drug release within 10 min. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity [19].

Jaber et al 2107 evaluated the protective efficacy of metoclopramide (MCP) against the organophosphates paraoxon (POX)- and malathion (MLT)-induced apoptosis in the murine L929 skin fibroblasts. L929 cells were exposed to either POX (10 nm) or 1.0 μm MLT in the absence and presence of increased concentrations of MCP. The protective effect of MCP on these organophosphate-stimulated apoptotic events was evaluated by flow cytometry analysis after staining with annexin-V/propidium iodide, processing and activation of the executioner caspase-3, cleavage of the poly-ADP ribose polymerase, fragmentation of the nucleosomal DNA and disruption of the mitochondrial membrane potential (Δψ). Our results showed that increased doses of MCP alone (≥10 μm) did not induce apoptosis or activation of caspase-3. Pretreatment of the cells with MCP attenuated all the apoptotic events triggered by the organophosphate compounds in a dose-dependent manner reaching ~70-80% protection when they were preincubated at 1 and 5 μm of the drug before the addition of POX and MLT, respectively. Interestingly, MCP did not offer a significant protective effect against the cytotoxicity of tumor necrosis factor-α, cisplatinum, etoposide or paclitaxel, which stimulate apoptosis by various mechanisms, suggesting that the anti-apoptotic effect of the drug is specific to organophosphates. The strong and specific anti-apoptotic activity of subclinical doses of MCP against the cytotoxicity of organophosphate compounds suggests its potential clinical application in treating their poisoning [20].

Epifanio et al 2017 carried out comparative study on the effectiveness of a single intramuscular dose of bromopride, metoclopramide, or ondansetron for treating vomiting. The outcome of present study reveals that a single dose of ondansetron is superior to bromopride and metoclopramide in preventing vomiting six hours and 24h following treatment. Oral fluid intake after receiving medication was statistically better with Ondansetronwhile also having less side effects compared to the other two agents [21].

CONCLUSION

Metoclopramide HCl is an anti-nauseated and antiemetic agent indicated for the prevention of nausea and vomiting associated with moderately-emetogenic cancer chemotherapy and for the prevention of postoperative nausea and vomiting. The chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine, and that the released serotonin then activates 5-HT3 receptors located on vagal efferents to initiate the vomiting reflex. Therefore Metoclopramide HCl works by blocking the reception of serotonin at these 5-HT3 receptors. Metoclopramide HCl has the half-life of 5-6 hours. Its total bioavailability in the body is 60% due to first pass metabolism. The total dose of Metoclopramide HCl is Oral: 0.5 mg/kg every 6 hours on days 2 to 4 hours before chemotherapy and repeat 2 hours after chemotherapy. In present review attempt had been made to covers all the aspect of works done on drug Metoclopramide including their pharmacological effect, pharmacokinetic parameters and work on analytical methods available for their determinations. The review also enlightens the recent work done on the drug Metoclopramide, which helps an extension of the work carried out on Metoclopramide in future.

REFERENCE:

1. Chue P, Welch R, Binder C. Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorders. Can J Psychiatry **2004**;49:701Y703.
2. Shu T, Suzuki H, Hironaka K, Ito K. Studies of rapidly disintegrating tablets in oral cavity using coground mixture of mannitol with crospovidone, Chem Pharm Bull (Tokyo) **2002**;50:193Y198.
3. Monograph. The American Society of Health-System Pharmacists. Retrieved **2014**-09-27.
4. Becker, WJ. Acute Migraine Treatment in Adults. Headache. **2015**;55(6):778–93.
5. Walter Sneader (31 October **2005**). *Drug Discovery: A History*. John Wiley & Sons. pp. 205.
6. FDA NDA no. 017862 - Approval history.
7. FDA NDA 017854 History of Approvals.
8. Staff, Virginia Historical Society. A.H. Robins Company; 24, **2016**.
9. Melody Petersen for the New York Times. March 11, 2002 American Home Is Changing Name to Wyeth
10. Staff, Emergency Physician Monthly. All About Metoclopramide (Reglan)
11. Besancou JL, Laville C, Thominet M. Le metoclopramide et ses homoloques: introduction a leur etude biologique. *C R Acad Sci (Paris).* **1964**;258:4384-6.
12. Pinder RM, Brogden RN, Sawyer PR, Speight TM, Avery GS. Metoclopramide: a review of its pharmacological properties and clinical use. *Drugs.* **1976**;12:81-131.
13. D. Nicholas Bateman. Clinical Pharmacokinetics of Metoclopramide. Clini Pharmacokin **1983**;8(6):523–529
14. Metoclopramide (met-oh-kloe-pra-mide) Metonia, Metozolv ODT, Reglan (REM).
15. *Dudhane N P et al,.* Simultaneous UV Spectrophotometric estimtion of Metoclopramide hydrochloride and Paracetamol in solid dosage form. *J Pharm Sci & Res **2010**;2(1):48-52*
16. Ahmad Khan, Syed Baqir Shyum Naqvi, Muhammad Harris Shoaib, Rabia Ismail Yousaf, Jallat Khan, Muhammad Hanif and Asadullah Madni. Validation and application of RP-HPLC method for the quantification of metoclopramide hydrochloride in oral formulations prepared for IVIVC studies. Pak J Pharm Sci **2012**;25(1):135-140.
17. KB. Patel, SN. Shete, VS. Belgamwar, AR. Tekade. Formulation design and optimization of tastemasked mouth-dissolving tablets of Tramadol hydrochloride. Asian J Pharm **2010**.
18. Dhima R, Sharma R. Formulation and *in vitro* evaluation of taste masked orodispersible tablet of metoclopramide hydrochloride using indion 204. Int J Chem Tech Res **2010**;2(1):447-453.
19. Goel H, Kaur G, Tiwary AK, Rana V. Formulation development of stronger and quick disintegrating tablets: a crucial effect of chitin. Yakugaku Zasshi **2010**;130(5):729-735.
20. Jaber BM, Petroianu GA, Rizvi SA, Borai A, Saleh NA, Hala SM, Saleh AM. Protective effect of Metoclopramide against organophosphate-induced apoptosis in the m murine skin fibroblast L929. J Appl Toxicol **2017**.
21. Epifanio M, Portela JL, Piva JP, Ferreira CHT, Sarria EE, Mattiello R. Bromopride, metoclopramide, or ondansetron for the treatment of vomiting in the pediatric emergency department: a randomized controlled trial. J Pediatr (Rio J). **2017**.

How to cite this article:

Swati Mishra et al. RECENT UPDATE ON METOCLOPRAMIDE: A REVIEW. J Pharm Res 2017;6(12):235-237. **DOI: https://doi.org/10.5281/zenodo.1135341**

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil