Drug Corner

Revisiting the Efficacy and Safety of Ranitidine

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Ranitidine, a competitive antagonist of histamine-2 receptors, has been widely prescribed for the treatment of peptic ulcer disease and mild to moderate reflux esophagitis for more than twenty years now. With its well-established tolerability and efficacy profiles, ranitidine is a preferred agent for initiation as well as maintenance of treatment in gastroduodenal conditions. Continuous maintenance treatment with ranitidine for up to nine years is known to prevent ulcer recurrence in more than 80% of patients with duodenal ulcer disease. Overall, ranitidine is well tolerated, and adverse and serious adverse events are rare with the use of ranitidine. Common ranitidine related adverse effects include headache, dizziness, diarrhea, and fatigue. None of these side effects require discontinuation of treatment and are generally self-limiting. Ranitidine is safe for use in elderly, pregnant women, and children. Given the current situation regarding the unacceptable levels of N-Nitrosodimethylamine, a probable human carcinogen, in ranitidine formulations, there are concerns about the clinical utility of ranitidine. In this review, we describe the efficacy and safety of ranitidine and the concerns for safety with the continued use of ranitidine. Given the widespread evidence for efficacy and safety, the concerns for safety with N-Nitrosodimethylamine in ranitidine formulations should be addressed with appropriate analytical assessment and judicious use.

[*J Indian Med Assoc* 2021; **119(11):** 66-73]

Key words **: Ranitidine, peptic ulcer disease, efficacy, safety, cancer.**

Introduced in 1981, ranitidine is a competitive antagonist of histamine-2 (H2) receptors that reduces gastric acid secretion. Ranitidine has been used in the short-term treatment of gastro-esophageal reflux disease (GERD) and endoscopically diagnosed erosive esophagitis, and in the maintenance therapy for duodenal or gastric ulcer at reduced dosage and erosive esophagitis. Short-term treatment with ranitidine is also effective in active duodenal ulcer or benign gastric ulcer, pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome and systemic mastocytosis). Ranitidine is extensively used in the management of these conditions with a key goal of reducing gastric acid secretion. It was one of the medicines after antibiotics to have had a profound impact in clinical practice. Given this widespread use, ranitidine is listed in the WHO model list of essential medicines[1]. Increased gastric acid secretion is a common clinical challenge presenting as either a non-specific complaint like heartburn or as a manifest inflammation or ulceration. Given the changing lifestyle with poor dietary choices and increasingly sedentary habits, increased gastric acid secretion is widely prevalent.

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Received on : 19/10/2021

Accepted on : 01/11/2021

Editor's Comment :

- Ranitidine enables a simple approach to reduce gastric acid secretion with rapid and reliable effect and reduced risk of recurrence.
- Ranitidine is safe for use in children, elderly, and pregnant women.
- More recent studies support no association of ranitidine with the risk of cancer.
- The proven efficacy and tolerability of ranitidine since its introduction over twenty years ago will ensure its continued use in the treatment of gastroduodenal conditions.

Ranitidine, with an effective suppression of acid secretion, is the preferred agent for reducing gastric acid secretion in clinical practice. The evidence suggests an excellent safety profile and a favorable risk/benefit ratio for ranitidine[2-4]. However, recently concerns have been raised from the safety point of view associated with ranitidine. This has challenged the clinical utility of ranitidine in the management of acid-peptic disorders. In this paper, we review the clinical efficacy and safety profile of ranitidine to reiterate the beneficial outcomes with ranitidine in peptic disorders. We also discuss here the current evidence and controversies published for the ranitidine formulations and how this could possibly impact the therapeutic utility of ranitidine in routine clinical practice for adults and children.

Efficacy of Ranitidine :

Ranitidine has a good efficacy in the management of gastroduodenal conditions. Ranitidine (150 mg twice daily for 6 weeks) is effective in reducing the frequency

and severity of heartburn and improving the endoscopic morphology of esophageal mucosa in gastroesophageal reflux disease[5]. Ranitidine has comparable efficacy to rabeprazole, a proton pump inhibitor, when used as an on-demand therapy for relieving symptoms associated with Non-erosive Reflux Disease (NERD). In a 4-week, prospective, randomized, open-label study in 83 patients with NERD, there was no significant difference in the subjective global symptom relief between the rabeprazole (n=40) and the ranitidine (n=36) groups (71.4% *versus* 65.4%, respectively; P = 0.9). There were comparable results for quality of life, mean numbers of pills used, and mean number of medication-free days for ranitidine and rabeprazole[6]. Combination of ranitidine with proton pump inhibitors is said to be superior to single drug treatment in laryngopharyngeal reflux[7].

Ranitidine is effective in erosive esophagitis. In a double-blind, placebo-controlled study in 342 patients with erosive esophagitis, ranitidine (150 mg and 300 mg four times daily) had significantly higher healing rates of 83% and 81%, respectively for the two doses and 58% for placebo at 12 weeks. The frequency, severity of heartburn and weekly intake of antacids were significantly reduced in the ranitidine arms and both doses were equally effective. Both doses demonstrated a rapid onset of action with symptom relief within 24 hours of medication intake[8]. Ranitidine (75 mg) is also effective in preventing and decreasing symptoms of heartburn when administered 30 minutes prior to intake of a heartburn-provoking meal[9].

Ranitidine is a commonly prescribed co-medication with Nonsteroidal Anti-inflammatory Drugs (NSAIDs) as it helps to reduce the dyspepsia, mucosal lesions, gastroduodenal disease, and ulcers associated with the use of NSAIDs. Ranitidine significantly increases the healing in NSAID-induced gastric and duodenal ulcers both during therapy and after discontinuation of NSAIDs[10]. It is also used a prophylactic option for gastroduodenal protection in patients who need long-term treatment with NSAIDs[11,12].

Ranitidine has demonstrated good efficacy in the management of gastroduodenal ulcers. A meta-analysis of 293 Randomized Clinical Trials (RCTs) in patients with duodenal ulcers demonstrated higher healing rates at 4 weeks with ranitidine when compared to other H2 receptor antagonists, antacids, colloidal bismuth, sucralfate, pirenzepine, and prostaglandin analogues. However, superior response was seen with omeprazole[13].

Ranitidine is an effective treatment for long-term maintenance therapy in duodenal ulcer disease. In a study in 464 patients with duodenal ulcer disease who received maintenance treatment with either 150 mg/day or 300 mg/day ranitidine for nine years, 95%, 88%, 86%, and 81% were free from symptomatic recurrence of ulcer at 1, 3, 5, and 7 and 9 years, respectively[14]. In this study, risk of hemorrhage in patients on maintenance treatment with ranitidine for nine years was less than 2% compared with greater than 12% in untreated patients who were observed for 5 years. In another multicenter study in 160 patients with endoscopically confirmed active duodenal ulcers who received maintenance treatment for six months with either 20 mg/day of famotidine or 150 mg/day of ranitidine, healing of ulcers was maintained in 79% of 58 famotidine-treated patients and in 81% of 52 ranitidine-treated patients[15].

Ranitidine is a preferred option for the long-term treatment of recurrent duodenal ulcer where it helps to reduce the risk of pain and discomfort and lowers the rate of recurrence. Eradication of Helicobacter pylori (H pylori) coupled with ulcer healing helps to reduce relapse rates. This is said to be an acceptable and potentially cost saving approach in the management of duodenal ulcers[16]. Kurata *et al* reported a higher chance of ulcer recurrence for cimetidine (400 mg HS) when compared to ranitidine (150 mg HS) for use over 12 months in seven clinical trials (OR:1.63; 95% CI: 1.21, 2.21). About 8.4% fewer patients experienced an ulcer recurrence on ranitidine ($p<0.01$)[17]. Continuous use of ranitidine as maintenance treatment in patients with healed duodenal ulcers sustains the healing of ulcers over long term[18,19]. The two-year GEMUD (Grouped'Etude de la Maladie Ulcéreuse Duodénale) study in 399 patients with duodenal ulcer supported the use of ranitidine (150 mg/day) for maintenance treatment. More patients in the ranitidine arm were free of endoscopic relapse when compared to placebo (83% *versus* 47%; $p <0.0001$)[19].

Role in H pylori Infection :

Ranitidine based triple regimens with antibiotics are used in the management of H. pylori infections. Triple regimen of ranitidine bismuth citrate (400 mg bd), amoxicillin (1 g bd), and clarithromycin (500 mg bd) is an effective therapy for the eradication of H pylori in dyspeptic patients. This regimen was found to have comparable eradication rates when compared to lansoprazole-based regimen (65.1% *versus* 63.6%)[20]. Mean H pylori eradication rates with 7-day ranitidine-clarithromycin-amoxicillin, ranitidine-clarithromycin-nitroimidazole, and ranitidine-amoxicillin-nitroimidazole are 83%, 86%, and 71%, respectively. Ranitidine and proton pump inhibitor-based regimens show

comparable efficacy for H pylori eradication when they were combined with clarithromycin and amoxicillin (OR: 1.11; 95% CI: 0.88-1.40), or with amoxicillin and metronidazole (OR: 0.92; 95% CI: 0.60-1.41). However, ranitidine based triple regimens show higher cure rates than proton pump inhibitor-based regimens when combined with clarithromycin and a nitroimidazole (OR = 1.65; 95% CI = 1.15-2.37)[21].

Safety of Ranitidine :

Ranitidine is well tolerated and has a good safety profile with a low incidence of adverse and Serious Adverse Events (SAEs). Overall, the incidence of general side effects at less than 2% is very similar to placebo. The most common adverse events reported with the use of ranitidine include headaches, tiredness, dizziness and mild gastrointestinal disturbance (eg, diarrhoea, constipation and nausea). These complaints rarely call for discontinuation of treatment. Cardiovascular side effects are extremely rare with the use of ranitidine. Some episodes of sinus bradycardia and atrioventricular blockade have been reported with rapid intravenous administration and these resolved with drug discontinuation[22,23].

Data from a large population of >26,000 patients in 189 controlled clinical trials (1979 to 1992) along with analyses of post marketing surveillance studies and spontaneously reported adverse events were reviewed to evaluate the safety of ranitidine after more than a decade of use. In this study, >80% patients received up to 300 mg/day dose of ranitidine. The most common organ systems involved in spontaneous Adverse Events (AEs) were central nervous system followed by skin hypersensitivity reactions, and gastrointestinal system (Fig 1). With prescription doses, the most common individual AEs with ranitidine were headache (3.3%), upper respiratory infections (2.1%), nausea or vomiting (1.8%), abdominal pain (1.7%), diarrhea (1.7%), and dizziness or giddiness (1.3%). SAEs (n=791) which were reported in 445 patient treatments (1.4% of total) with an overall frequency of =1%. There were no significant differences in the frequency of SAEs with ranitidine or placebo (Fig 2)[24].

Events have been reported based on estimate of 209 million patient treatments dispensed world-wide after over a decade of use since its launch in 1981.

A small proportion of patients may develop an idiosyncratic reaction shortly after the start of treatment with ranitidine, but continuous, long-term treatment is not associated with any reactions[23]. Tachyphylaxis is known to occur after a long-term use of ranitidine and this can develop within 14 days[25]. However, tolerance to initial dosing with ranitidine is not a progressive phenomenon during continued dosing. A placebo-controlled prospective study in healthy subjects has shown that the antisecretory activity of a maintenance dose of ranitidine (150 mg once daily at night) remains relatively constant between the first and fifth months of continuous dosing[26].

The use of proton pump inhibitors over long time warrants vigilance as there is an increased risk of mortality. In a longitudinal observational study in the US Department of Veterans Affairs in new users of proton pump inhibitors (n = 157 625) or H2 blockers (n = 56 842), more deaths were observed in those taking

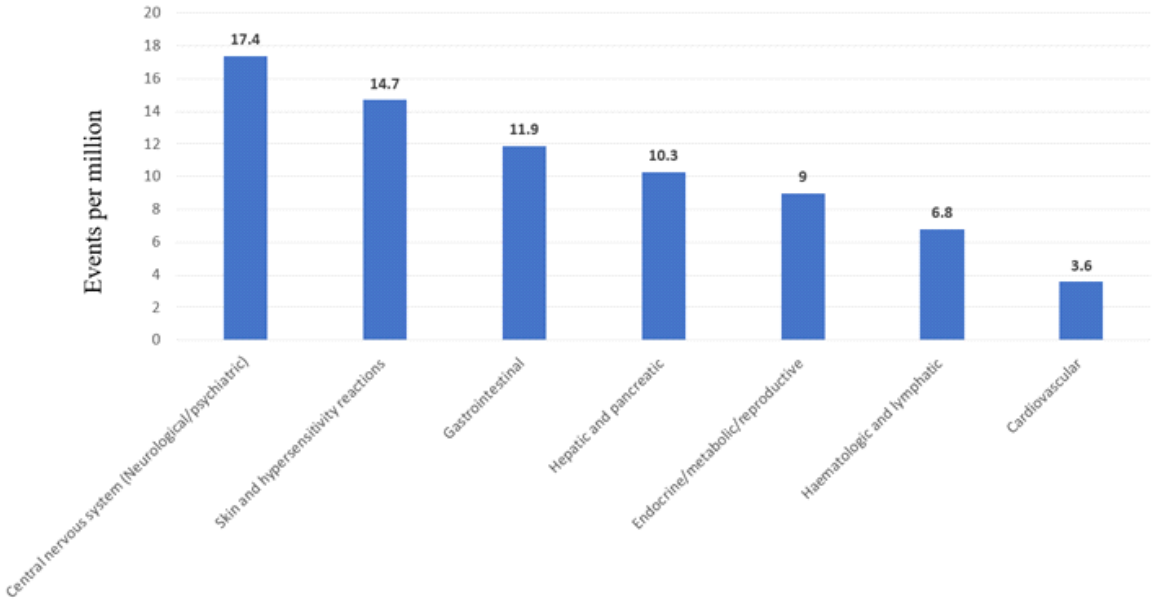

Fig 1 — Organ system review for worldwide spontaneous adverse events with ranitidine use

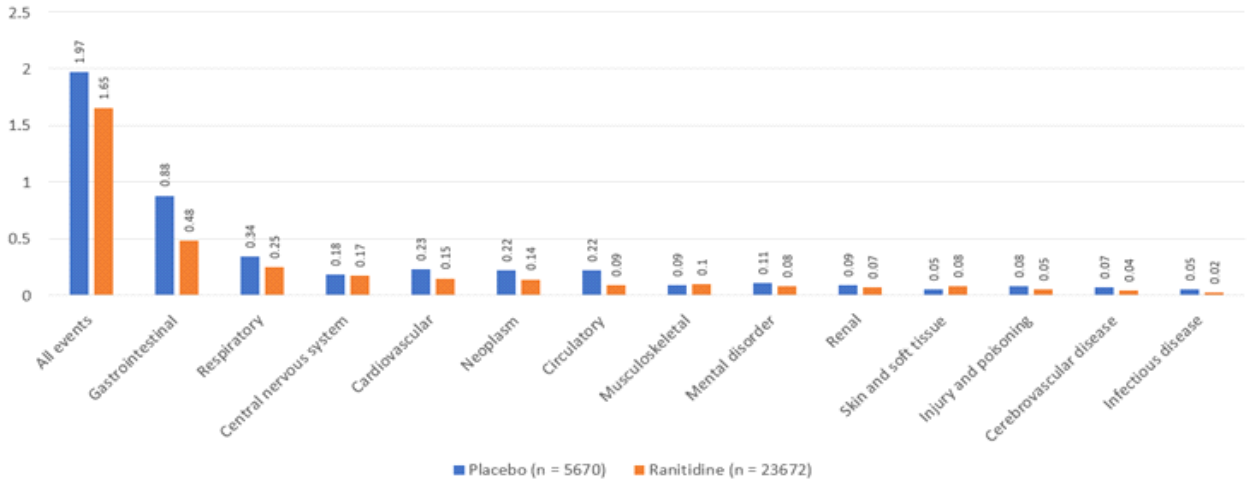

Fig 2 — Incidence of serious adverse events (percentage) with over a decade of use of ranitidine since 1981

proton pump inhibitors than in those taking H2 blockers (37.92% and 35.69%, respectively) over a median duration of follow up of 10 years (interquartile range 6.95-10.00)[27]. Using big data to emulate a target trial, the authors reported excess mortality due to cardiovascular disease (number of attributable deaths per 1000 PPI Users: 22.91, 95% CI: 11.89 to 33.57), chronic kidney disease (4.74, 95% CI: 1.53 to 8.05), and upper gastrointestinal cancer (3.12, 95% CI: 0.91 to 5.44) in a comparative analysis for the new use of proton pump inhibitors versus H2 blockers on the cause-specific mortality Among patients without documented indication for acid suppression drugs (n = 116 377).

Ranitidine in special populations :

Elderly : Ranitidine is safe for use in the elderly. In a retrospective review of 21 placebo-controlled trials in 4041 patients who received 150 – 300 mg/day dosage of ranitidine for 4 to 52 weeks, no significant differences were seen in the incidence of AEs in elderly (=65 years) or younger (<65 years) patients who received ranitidine or placebo[2].

Pregnant women : GERD is common in pregnant women and ranitidine has been used for this condition in doses of 150 mg twice daily for 4 weeks. The use of ranitidine during the first trimester of pregnancy is not associated with a major risk of teratogenesis. In a review of data of the United Kingdom General Practice Research Database and the Italian Friuli-Venezia Giulia Health Database (1991-1996), the relative risks for nongenetic congenital malformations associated with the use of cimetidine, omeprazole, and ranitidine were 1.2 (95% confidence interval (CI): 0.6, 2.3), 0.9 (95% CI: 0.3, 2.2), and 1.4 (95% CI: 0.8, 2.4), respectively, in first trimester-exposed pregnancies compared with the nonexposed pregnancies[28].

The National Birth Defects Prevention Study (NBDPS), a population-based case-control study (4524 cases and 5859 controls from September 1997 to December 2004), evaluated the association of pharmacotherapy for nausea and vomiting in pregnancy with non-cardiac defects in offsprings. The adjusted odds ratios (aOR) of cleft lip with or without cleft palate in offspring exposed to H2 blockers in the first trimester was 0.57 (95% CI: 0.19–1.67). The aOR for cleft palate with H2 blockers, ranitidine, and proton pump inhibitors were 1.04 (95% CI: 0.39–2.75), 1.33 (95% CI: 0.49–3.61), and 2.59 (95% CI: 0.88–7.63), respectively. The aOR for neural tube defects with H2 blockers and ranitidine were 1.80 (95% CI: 0.80–4.05) and 1.28 (95% CI: 0.43–3.82), respectively. In this study, proton pump inhibitors were associated with an increased risk for hypospadias (aOR=4.36, 1.21–15.81) when compared to H2 blockers (aOR: 1.07; 95% CI: 0.41–2.83 and ranitidine (aOR: 0.70; 95% CI: 0.20–2.41)[29].

In a prospective study, pregnancy outcomes were compared for 230 pregnant women with gestation H2 blocker use (71% women received ranitidine) and 178 controls who were matched for age, smoking, and alcohol consumption. The most common indications for H2 blocker use were heartburn (415), peptic ulcer disease (30%), epigastric pain (175), and others (12%). There was no increase in major malformations following first trimester exposure to H2 blockers. Major malformations were seen in 2.1% women who took H2 blockers and 3.5% controls[30].

Children: Ranitidine has been widely used for various peptic disorders in children and is approved

for the treatment of GERD and healing of erosive esophagitis in children one month or more. It is also available in palatable formulations for administration in infants and children including syrup and effervescent tablets[31]. Ranitidine has been used for the treatment of functional dyspepsia in children[32]. Further studies are needed to define the efficacy of ranitidine in the long-term management of GERD in children[33].

Risk of carcinoma with use of ranitidine :

In April 2020, the U.S. Food and Drug Administration (FDA) called for an immediate withdrawal of ranitidine from the market. This was due to unacceptable levels of N-Nitrosodimethylamine (NDMA), a probable human carcinogen, in ranitidine medications[34]. However, more recent evidence does not support this finding. In an in vitro study with simulated gastric fluid with different nitrite concentrations suggested that ranitidine was not converted to NDMA in gastric fluid at physiologic conditions. Ranitidine (1 tablet of 150 mg) was not converted to NDMA until nitrite was 5000 µmol/L, a level about 50-fold greater than the upper range of physiologic gastric nitrite concentrations at acidic pH[16]. In a recent crossover, RCT in 18 healthy participants, urinary NMDA excretion was compared for oral ranitidine (300 mg) and placebo. The median 24-hour NDMA urinary excretion values for ranitidine and placebo were 0.6 ng (interquartile range [IQR] 0-29.7) and 10.5 ng (IQR 0-17.8), respectively, with a noncured meats diet, and 11.9 ng (IQR 5.6-48.6) and 23.4 ng (IQR 8.6-36.7), respectively, with a cured meats diet.35This study did not support the conversion of ranitidine to NDMA in healthy adults. Limitations of the study include the study population of healthy adults who may have different gastric pH when compared to patients with acid reflux or ulcers and the administration of ranitidine with breakfast which may impact the saliva sources of nitrites.36Further, a study published in 2016, reporting an increase in urinary excretion of N-NMDA after ranitidine ingestion was recently retracted in 2021[37].

An observational population-based cohort study evaluated the risk of cancer following the use of N-NMDA contaminated ranitidine products in 40,488 ranitidine users (January 2009 – December 2011) from the Health Insurance Review and Assessment (HIRA) database in South Korea[38]. This study constructed a 4:1 matched cohort of 10122 famotidine users as no NMDA has been detected in famotidine. During a follow up period of seven years, there was no risk of cancer with exposure to NMDA exposure through ranitidine as no statistical difference in the overall cancer risk in short-term was seen in the ranitidine and famotidine groups (7.45% *versus* 7.56%; HR: 0.99; 95% CI: 0.91–1.07, p= 0.716).

H2 receptor antagonists are not associated with an increased risk for cancer with long-term use for benign or malignant gastroduodenal conditions. Patients with gastric cancer may present with symptoms similar to benign gastric acid and may receive treatment with H2 receptor antagonists. In a case control study in Italy in patients with newly diagnosed, histologically confirmed gastric cancer (n = 563) were compared to 150 controls without the malignancy who received either cimetidine or ranitidine. In this study, the risk of gastric cancer was not increased over 5 years or more in these patients though there was an increased risk in the initial few years of initiation of treatment[39].

A population-based study in Sweden (2005-2012) compared long term maintenance therapy (defined as at least 180 days during the study period) with proton pump inhibitors and H2 receptor antagonists for the risk of gastric cancer. In this Swedish prescribed Drug Registry, the Standardized incidence ratio (SIR: 3.38, 95% CI: 3.23 to 3.53) for gastric cancer increased by over threefold in 797067 individuals who received proton pump inhibitors for maintenance. When standardized for indications, the risk for gastric cancer was not increased in long-term users of H2 receptor antagonists[40]. In an assessment for the risk of esophageal cancer with the two treatment options, in patients who received maintenance therapy with only histamine-2-receptor antagonists (n = 20177), there was no increased risk of esophageal adenocarcinoma (SIR: 0.39, 95% CI: 0.04–1.40, n = 2) or esophageal squamous cell carcinoma (SIR: 0.50, 95% CI: 0.06–1.88, n = 2)[41].

More recent studies support no association of ranitidine with the risk of cancer.

Yearly incidence of new gastrointestinal malignancies was obtained for 10 years in users of ranitidine, famotidine, and omeprazole from the nationwide database IBM Explorys in the US. This study did not show increased odds of gastrointestinal malignancies with ranitidine compared to famotidine or omeprazole (Fig 3)[42]. In an analysis of the Japan Medical Data Center Claims Database (2005-2018), there was no evidence for an increased risk of cancer with ranitidine or nizatidine compared with cimetidine, famotidine, roxatidine, and lafutidine; the adjusted hazard ratio (ranitidine/nizatidine users vs other H2 blocker users) was 1.02 (0.98-1.07)[43]. A retrospective, nationwide cohort study (May 1, 1998 to December

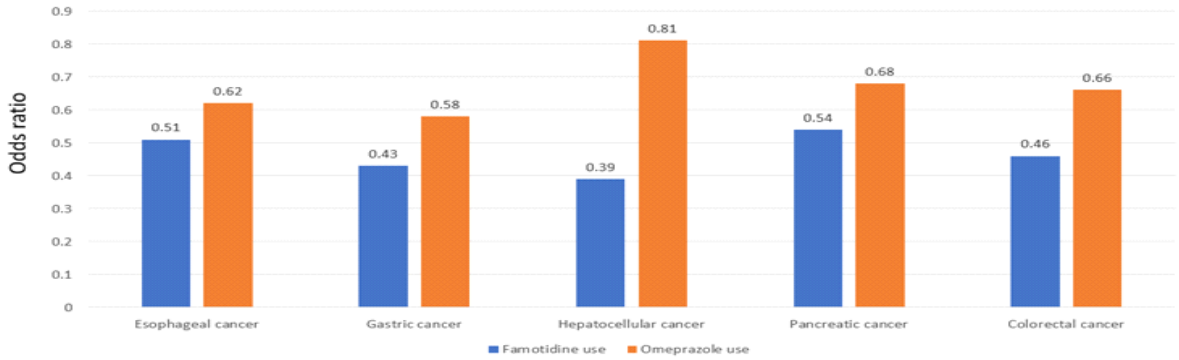

Fig 3 — Risk of gastrointestinal malignancies with use of ranitidine when compared to use of famotidine or omeprazole

31, 2018) in 279,505 patients within the Veterans Health Administration who had a H pyloriinfection and were prescribed long-term acid suppression demonstrated no association between ranitidine use and future gastric cancer. The users of non-ranitidine H2 blockers were more likely to develop gastric cancer when compared to the users of ranitidine (HR: 1.83; 95% CI: 1.36-2.48)[44]. In a large prospective nationwide Danish Prescription Registry with 103,565 first time users of ranitidine and 182,497 and 807,725 incident users of other H2 receptor blockers and proton pump inhibitors, respectively, there was no consistent evidence of increased risk of any upper gastrointestinal cancer following ranitidine use[45].

Conclusions :

Ranitidine is widely used to reduce gastric acid secretion in conditions like gastric and duodenal ulcers, gastroesophageal reflux, and esophagitis. In these conditions, the use of ranitidine enables a simple approach to treatment with rapid and reliable effect and a safe treatment with reduced risk of recurrence. Ranitidine's safety has been proven for use in children, elderly, and pregnant women. The efficacy and tolerability of ranitidine since its introduction over twenty years ago will ensure its continued use in the treatment of gastroduodenal conditions. Given the recent concerns with ranitidine, clinicians have a choice to discontinue treatment with ranitidine or switch to an alternative therapy based on clinical discretion, patient's conditions, and any apprehensions of the patients or their families for the use of this long-trusted drug[46].

Acknowledgement

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

Medical writing and editorial support in the preparation of this article was provided by Dr. Tarveen Jandoo of Mediception Science Pvt Ltd (www.mediception.com).

Conflict of interest : **None**

Funding : **None**

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