International Digital Organization for Scientific Research ISSN: 2579-0781
IDOSR JOURNAL OF EXPERIMENTAL SCIENCES 9(1) 68-71, 2023.

A Review on Cimetidine and its Toxicological Effects on Male Reproductive System

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ABSTRACT

Cimetidine is recommended for the treatment of chronic peptic ulceration, haemorrhage from erosive gastritis, and the control of gastric hypersecretion and peptic ulceration in the Zollinger-Ellison syndrome, cimetidine1 is a specific competitive histamine H2-receptor antagonist that effectively inhibits gastric acid secretion. Therefore, this review further highlights the mechanisms of action, adverse effect profile, and other significant elements important to the interprofessional team members in patient management utilizing cimetidine.

Keywords: Cimetidine, peptic ulcer, haemorrhage and Zollinger-Ellison syndrome

INTRODUCTION

Cimetidine is an anti-ulcer medication that is a member of the class of drugs known as Histamine H2 receptor antagonists. It functions by lessening the stomach's acid production. Additionally, GERD, peptic ulcer disease, and indigestion are managed with it. It produces the exact reverse of what histamine should have done when it blocks histamine receptors. It is an excellent medication for the treatment of ulcer because it also stops histamine from activating vascular endothelia growth factor (VEGF), which stops angiogenesis in granulated tissue [1]. Dihydrotestosterone (DHT) and cimetidine aggressively compete for receptor space in the tissues of the pituitary and hypothalamus, which has an anti-androgenic impact [1]. The chemical formula for cimetidine is C10H16N6S, with a molecular average weight of 252.339/mol.

Cimetidine is a highly effective medication that is widely used to treat gastric and duodenal ulcers [2]; [3]; [4]. An over-the-counter histamine (H2) receptor blocker called cimetidine is frequently used to treat stomach ulcers. It achieves its function by preventing the parietal cells of the stomach's gastric juice from secreting gastric juice, alleviating the patient of the gastric discomfort that results from gastric acid secretion [4]. Cimetidine is an H2-receptor antagonist that inhibits the action of histamine on H2-receptors in the parietal cells of the stomach, preventing the generation of acid, but it damages the testicles in the process. [4]; [5] & [6]. Despite the wide use and effectiveness of this drug, there have been several reports of its detrimental effects on the reproductive system in males.

Cimetidine'spharmacological indication, pharmacodynamics, and mechanism of action

Cimetidine is prescribed to treat the following conditions: pathological hypersecretion linked to Zollinger-Ellison Syndrome, systemic mastocytosis, and numerous endocrine adenomas; duodenal ulcers; non-malignant stomach ulcers; gastroesophageal reflux disease; and these conditions [7]. It is prescribed to prevent recurrent stomach or duodenal ulcers, treat NSAID-induced lesions and gastrointestinal symptoms in patients with cystic fibrosis, and prevent recurrent gastric or duodenal ulcers in adults [7].

As a histamine H2-receptor antagonist, cimetidine lowers baseline and nocturnal stomach acid secretion as well as the quantity of acid produced in response to

stimuli like food, coffee, insulin, betazole, or pentagastrin [7]. It is used to treat gastrointestinal problems like pathological hypersecretory syndromes, gastric or duodenal ulcers, and gastroesophageal reflux disease. Numerous isoenzymes of the hepatic CYP450 enzyme system are inhibited by cimetidine. An increase in the gastrointestinal bacterial flora, such as nitrate-reducing organisms, is one of Cimetidine's additional effects.

The effects of histamine are blocked by cimetidine when it binds to an H2-receptor on the basolateral membrane of the stomach parietal cell. Reduced stomach acid output, decreased gastrointestinal volume, and decreased acidity are all effects of this competitive inhibition.

When histamine is produced during a typical physiological event, it interacts to histamine receptors (H2) and causes an increase in cyclic adenosine monophosphate (cAMP), which activates the hydrogen pump found in parietal cells called H+ K+- ATPase. The stomach's parietal cells respond by secreting gastrin, acetylcholine, or histamine in response to stimulation. When physiological processes activate G-protein coupled receptors, histamine is essential (H-1, 2, 3 &4). H2 receptors control stomach acid secretion, moderate intestinal motility, secretions, cell proliferation, and relaxing of vascular smooth muscle [1].

Due to its propensity to inhibit histamine receptors, cimetidine may cause reproductive damage by interfering with testosterone's ability to convert to its active form, dihydrotestosterone [4].

Examining the evidence for cimetidine

For treating peptic ulcers, cimetidine is still a crucial medication that is prescribed on a global scale. Since the nature of the disease being treated necessitates long-term treatment, the medicine is typically given for long-term usage. Therefore, the clinical significance of the reprotoxicity caused by cimetidine necessitates preventative or therapeutic intervention [8].

Cimetidine after being administered orally, cimetidine was said to be absorbed in the abdomen. This drug's bioavailability when taken orally indefinitely has been estimated to be up to 70% higher than when administered intravenously. Once the drug has been processed in the liver and eliminated through the urinary system in urine, it has a half-life of around two hours. The data collected from each man and animal study is consistent. Rats and dogs are therefore appropriate animal models for using in experiments involving antacid exposure in humans, and their usage in studies of repro-toxicity is even more appropriate [9].

Although this medication is widely used and effective, there have been several reports of its harmful effects on male reproductive systems, leading to its classification as a reproductive toxicant. Cimetidine has certain unfavorable effects on reproduction, such as altering testicular histoarchitecture, significant seminiferous tubule degeneration, maturation arrest of spermatogenic cells, reductions in sperm motility and count, and impotence, which reduces sexual urge and desire [10]; [11];[12] [17]; [18]; [19] [20].

Oyebola, [13], conducted a study on the effect of ethanol extrat of vernonia amygdalina (del.) leaf on cimetidine-induced reproductive toxicity in male wistar rat the result of the study showed a significant decrease in body weight change (%), sperm motility (%) viability (%) and count (106/ ml) as well as significant increase in relative testicular (g), epididymal (g), seminal vesicle weight (g) and abnormal sperm in the groups treated with secnidazole.

In comparison to the control, the LH level rose while the FSH level and testosterone level fell, respectively. Photomicrographs of the testis and epididymis revealed cellular erosion, enlargement of the lumen of interstitial cells, and vacuoles. In 2014, Aprioku, Ibeachu, and Ijeomah undertook a study on the protective effect of ascorbic acid on cimetidine-induced reproductive toxicity in male wistar rats. Their study revealed that cimetidine can

have a number of adverse effects, including a significant and dose-dependent decrease in sperm count and motility. Although there was no change in the morphology or viability of the sperm, there were changes in the testis' histology, including substantial seminiferous epithelium degradation, spermatogenic cell vacuolization and maturation arrest, as well as changes to testicular function.

The study of Xu *et al.* [14] evaluated the effect of oral cimetidine on the reproductive system of male wistar rats revealed that sperm average path velocity, straight line velocity and curvilinear velocity were significantly decreased in the 120mg/kg cimetidine group while luitenizing hormone and testosterone levels were significantly higher compared to the control group. While examining cimetidine as a reproductive toxicant in male wistar rats affecting peritubular cells, Luiz *et al.* [15] revealed that accessory sex organ weights but not testis weight were significantly reduced in the high dose treated groups, FSH level significantly elevated in both treated but the testosterone levels were unchanged. Additionally, in the high dose group, the volume of peritubular tissues decreased. Both severely injured tubules and those that appeared to be undergoing normal spermatogenesis both had substantial duplication of the inbasal lamina, lamina densa, and apoptotic peritubular myoid cells were also present.

In a study on curcuma longa's normalization of cimetidine-induced pituitary-testicular dysfunction: relevance in nutraceuticals, Ngozi *et al.* [16] found that cimetidine was linked to harmful changes in sperm motility, sperm count, and sperm vitality, as well as abnormalities in the plasma levels of FSH, LH, and testosterone at (p0.05). In addition, distortions in pituitary and testicular histo-architecture as well as significant changes in brain and testicular GSH and Tbars levels were seen after cimetidine administration.

Given the widespread use of cimetidine, allegations of its harmful effects on male fertility, and a rise in male infertility, which was previously thought to account for around 50% of cases [6]. A decrease in the weight of the testis and accessory glands was additionally seen in a laboratory experiment on rats [2]. Additionally, a different experiment revealed that the structural integrity of the testis and vas deferens had been compromised [1].

Cimetidine is known to target the hypothalamic-pituitary-testicular axis in males, which is associated with structural abnormalities in the testes' histology, though the exact mechanism by which it causes reproductive damage is unknown [10]. Therefore, we proposed the possibility that people with cimetidine-induced reproductive toxicity may be treated with intervention(s) that have positive effects on both gastrointestinal and reproductive processes in order to restore normal reproductive function.

CONCLUSION

This review study concluded that cimetidine is hazardous to male reproductive system.

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