CHAPTER I

1. Introduction

1.1. General introduction

1.1.1. Commencement

Histamine is a β-imidazolylethylamine derivative and essentially present in all mammalian tissues and organs, especially abundant in the lung tissue and in the skin. Also it occurs in the marrow and in the subcortex. A large quantity of histamine is produced and deposited in the mast cells of connective tissue, where it is stored in abound state as a protein-heparine complex. It is produced in large amounts in the gastric mucosa and it is always present with small amounts in the blood plasma and other biological fluids. It was synthesized[1] in 1907 before its presence in the tissues was recognized. Dale and Laidlaw[2-4] outlined the principal pharmacological activities of histamine from 1910-1919. After more than half a century of painstaking study, several physiological roles had been proposed for histamine[5].

Histamine probably plays a basic role in the beginning of the inflammatory response of tissue to injury by dilating the capillaries and increasing their permeability. The usefulness of this effect usually leads to a "walling off" of the area of injury[6]. Histamine exerts a verity of actions on the cardio-vascular system[7], plays a role in anabolic processes[8], acts as a central neurotransmitter[5,9], and plays a role in gastric secretion[10].

In general, histamine appears to be necessary for many physiological processes. Possibly, histamine has a homeostatic role and

the histamine-forming capacity of various tissues is responsive to alterations in the concentration of the amine. However, certain conditions may lead to excessive production or release of the autacoid (self medicinal agent) that causes expansion of capillaries, probably by constricting the smaller veins and causes a local edema and an increase in the volume of the vascular bed. The resulting drop in blood pressure, if severe enough, may induce shock. Less drastic action of histamine are implicated in other diseases, such as peptic ulceration and asthmatic condition. Therefore, these and other actions of histamine have been studied for the purpose of developing drugs that will block selectively certain actions of histamine. Because the antihistaminics inhibited some but not all of the actions of histamine, there must be more than one type of histaminic receptor.

In 1972, Black et al.[11] could differentiate the histamine receptors into H_1-receptors and H_2-receptors. Briefly, the pharmacological distinction of histamine receptors rests upon the action of histamine and its antagonists. Histamine stimulates the contraction of smooth muscle from various organs such as the gut and bronchi. Because low concentrations of antihistaminic drugs suppress this effect, the pharmacological receptors that mediate this response are referred to as H_1-receptors and the drugs are said to be H_1-antagonists. Also, histamine stimulates the secretion of acid by the stomach, increases the heart rate, and inhibits concentrations in the rate uterus. Because the classical antihistaminics do not antagonize these effects, the receptors that mediate these actions are said to be H_2-receptors. Likewise, drugs that inhibit these responses to histamine are classified as H_2-antagonists. In 1992, Leurs et al.[12] pointed out the most recently histamine H_3- receptor, which has been described to play a role as a general regulatory receptor

system, modulating not only the release and synthesis of histamine but also the release of other neurotransmitters. Studies with different experimental agents suggest that H_3-receptor agents might provide new therapeutics for central nervous system (CNS), airway, and gastrointestinal disorders. In our work, we will concentrate on the H_2-antagonists.

The discovery of H_2-antagonist burimamide in the early 1970's opened a new era in the history of the attempt to explain histamine-related physiological processes. Only history can record the importance of this discovery toward delineation of the role of histamine, as well as that of other autacoids, in homeostasis and disease. For more details there are literature surveys edited by Rocha e Silva[13] and by Fordtran and Grossman[14]. All H_2-receptor antagonists heal gastric and duodenal ulcers by reducing gastric acid output as a result of H_2-receptor blockade; like cimetidine and ranitidine and the newer one famotidine, can also be expected to relieve peptic oesophagitis. High doses of H_2-receptor antagonists have been used in the Zollinger-Ellison syndrome, but omeprazole may now be perferred

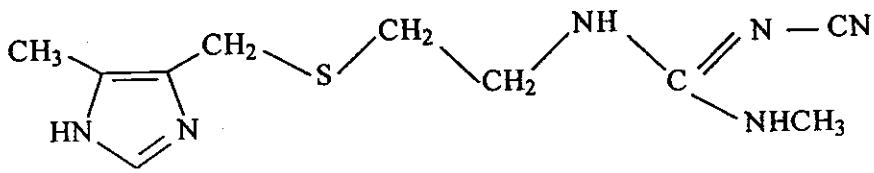
1.1.2. Investigation of the studied drugs

1.1.2.1. Cimetidine

Cimetidine is an effective histamine H_2-receptor antagonist drug which inhibits the secretion of basal and gastric acid and also reduces the out put of pepsin. It is like histamine, contains an imidazole ring with apparent pK_a of 6.8[15]. The drug is extensively used in the treatment of duodenal and gastric ulcers, in the management of reflux esophagitis and for the inhibition of gastric acid secretion associated with Zollinger-Ellison syndrome[16-21].

It is excreted as the unchanged drug (56-85%) and as hydroxymethyl, sulfoxide or guanylurea metabolites[17].Side effects appear minor such as mental confusion, cardiovascular problems, anti-androgenic properties, and blood dyscrasias[22-26]. The compound is given orally as a tablet and syrup, and as an injection fluid.

Chemical Structure:



Empirical Formula : $C_{10}H_{16}N_6S$

Chemical Name: 2-Cyano-1-methyl-3-[2-[[(5-methylimidazole-4-yl) methyl]thio]-ethyl]guanidine. [CAS: 51481-61-9].

Molecular weight: free base 252.352 and its hydrochloride salt 288.816.

Appearance: The free base and hydrochloride salt are white crystalline solids with little or no odour. A slight sulfur-mercaptan odour may be present.

Melting range: 139-144 °C.

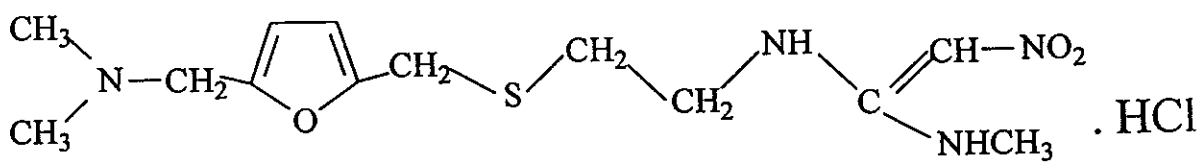
Solubility: It is very soluble in methanol and ethanol; and slightly soluble in water (1.14% at 37 °C). The solubility is greatly increased with the addition of dilute acid to protonate the imidazole ring[14].

1.1.2.2. Ranitidine

Ranitidine is a potent histamine H_2-receptor antagonist which is a hydrophilic molecule containing an aminomethyl furan derivative[27,28], with pK_a values of 2.7 (side chain) and 8.2 (dimethylamino). It has been reported to be 5-10 times more potent, on a molar basis, than cimetidine in inhibiting gastric acid secretion in man[29,30]. The degree of inhibition being directly related to the plasma concentration of the drug. Thus, an

inhibition of approximately 50% in acid secretion has been achieved with plasma concentrations of 100 ng ml^{-1} [31]. The drug is primarily excreted in urine and 60% or more may appear in the urine without modification with most of the remaining products being oxidation metabolites. It has fewer side effects and rarely happened such as tachycardia, agitation and visual disturbances, so considered to be the drug of choice for the treatment of duodenal and gastric ulcer patients[32,33]. It is also used in treatment of the Zollinger-Ellison syndrome[34-36] because of its increased potency and lesser effect on endocrine function compared to cimetidine. The compound is given orally as a tablet, and as an injection solution. The first synthesis of ranitditne was reported in 1973[17], followed by pharmacological and clinical studies in 1979[27,38] and 1980[39-41], finally ranitidine was introduced on the market in 1981.

Chemical Structure :



Empirical Formula: $C_{13}H_{22}N_4O_3S.HCl$.

Chemical Name: 2-[[[5-(dimethylamino)-methyl-2-furanyl]methyl]thio] ethylamino-2-methylamino-1-nitroethene [CAS: 66357-59-3].

Molecular weight: hydrochloride salt 350.869.

Appearance: Ranitidine base is difficult to crystallize, but its hydrochloride can be conveniently crystallized, practicularly from isopropanol so ranitidine is marked only as the hyrochloride salt. It is a white to yellowish solid with little or no odour. A slight sulfur-mercaptan odour may be present.

Solubility: It is very freely soluble in water and freely soluble in acetic acid and methanol and sparingly soluble in ethanol.

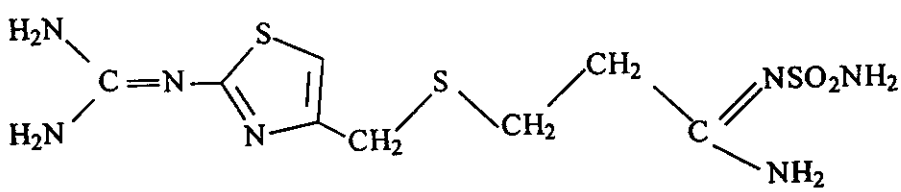
Melting range : 133-143 °C.

1.1.2.3. Famotidine

Famotidine is a relatively new histamine H_2-receptor antagonist having a structure related to that of cimetidine and ranitidine but having a thiazole ring. On a weight basis famotidine is twenty times more potent than cimetidine in inhibiting basal and pentagastrin-simulated gastric acid secretion in humans[42-44]. It is now widely used for the treatment of duodenal ulcers, benign gastric ulcer, reflux oesophagitis, and hyper-acid secretory conditions such as Zollinger-Ellison syndrome[45,46].

Famotidine is incompletely absorbed (40% to 45% bioavailability). As therapeutic doses of famotidine recommended in patients are low (40 mg daily), so these doses produce very low therapeutic concentrations in plasma[47, 48] (78 ng ml^{-1}). The drug is eliminated by renal (65% to 70%) and metabolic (30% to 35%) routes. Famotidine sulfoxide is the only metabolite identified in humans. It has fewer side effects and rarely happened such as: anxiety, urticaria, anorexia and dry mouth.

Chemical Structure:



Empirical Formula: $C_8H_{15}N_7O_2S_3$

Chemical Name: 3-[(2-guanidinethiazol-4-yl)-methylthio-]N-sulfamoyl propionamidine [CAS: 76824-35-6].

Molecular weight : 337.450

Appearance: Famotidine is a white or yellowish-white, crystalline powder or crystals, with little or no odour.