CHAPTER II

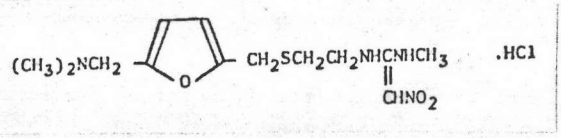
REVIEW OF RANITIDINE

Ranitidine, a new histamine H_2-receptor antagonist, has been widely used in the treatment of gastric and duodenal ulceration. The first synthesis of drug was reported in 1973 followed by pharmacological and clinical studies in 1979 and 1980. Finally, ranitidine was introduced on to the market in 1981 under the proprietary name Zantac® by Glaxo Operation. (14)

1. Physicochemical Properties (14, 15)

Name :	Ranitidine
Chemical name :	N,N-Dimethyl-5-[2-(1-methyl amino-2-nitrovinylamine) ethylthiomethyl] furfuryl amine
Description :	Ranitidine is marketed only as the hydrochloride salt. It occurs as a white to pale yellow granular substance having a slightly bitter taste and sulfur-like odor.
Empirical formula :	$C_{13}H_{22}N_4O_3S.HCl$

Structural formula :



Molecular Weight : 314.41 and 350.87 (ranitidine hydrochloride) Each 168 mg of ranitidine hydrochloride is approximately equivalent to 150 mg of ranitidine.

Melting Point : 133-134 °C

Solubility : Ranitidine hydrochloride has solubilities of 660 mg/ml in water, 190 mg/ml in methanol, 13.1 mg/ml in ethanol and 4.3 mg/ml in chloroform. The drug has pKas of 8.21 and 2.26

2. Pharmacological Effects (8, 15)

Ranitidine is a specific, rapidly acting histamine H_2-antagonist. It inhibits basal and stimulates secretion of gastric acid, reducing both the volume and the acid, and pepsin content of the secretion. Furthermore, it may protect the gastric mucosa from bleeding and the irritant effects caused by certain drugs. (eg., aspirin, nonsteroidal anti-inflammatory agents)

Ranitidine, unlike cimitidine, has no antiandrogenic effects and does not alter hepatic metabolism of drugs.

3. Therapeutic Indications (15)

Ranitidine is used for the short-term treatment of proven gastric ulcer and duodenal ulcer. Maintenance therapy with ranitidine has been used for reducing ulcer recurrence. Moreover, the drug is also used for the treatment of pathologic GI hypersecretory conditions. (e.g. Zollinger-Ellison syndrome, systemic mastocytosis, postoperative hypersecretion)

4. Pharmacokinetics

Absorption :

Ranitidine is rapidly absorbed from GI tract following oral administration. After a 150-mg oral dose, mean peak plasma concentrations are about 400 ng/ml and occur within 2-3 hours (8, 15, 16). Leeder et al. (17) reported that a mean value following 150 mg ranitidine in 6 subjects were 672 ng/ml within 3 hours. Absorption and mean peak plasma concentration of the drug are not affected by food or by the concurrent administration of antacid (8, 16, 18).

Bioavailability :

The absolute bioavailability of orally ranitidine has been reported to be about 50% and increased in patients with chronic liver disease (15). Smith et al. (19) found that the estimated systemic availability of ranitidine after 150 mg orally in normal and cirrhotic patients were 58 $\pm$ 11 % and 70 $\pm$ 7 %, respectively.

Distribution :

Ranitidine is widely distributed throughout the body, Plasma protein binding of ranitidine as determined by an equilibrium dialysis method ranged from 10-19 % in several studies (20, 21). The apparent volume of distribution of ranitidine is reported to be 1.2-1.9 L/kg (8, 12, 13, 15, 22). The drug penetrates very poorly into the cerebrospinal fluid but is concentrated into breast milk (15).

Metabolism and Excretion :

Information on metabolism of ranitidine after oral administration is incomplete. Its major metabolite is an N-oxide and there are smaller quantities of S-oxide and desmethyl ranitidine (15). It has been found that ranitidine does not inhibit the microsomal drug oxidative function

(8, 15, 23, 24). Ranitidine is excreted via the kidneys mainly as the free drug and in minor amounts as metabolites. The 24-hour urinary recovery of free ranitidine and its metabolites is about 40% with orally administered drug. The remainder is eliminated in feces, apparently via biliary excretion (15). Renal clearance is reported to be approximately 600 ml/min (15). The elimination half-life of intravenously administered single dose ranitidine is 1.6 to 2.1 hours (13, 20, 21) and is generally slightly longer after oral administration.

Recent studies of the relationship between plasma concentration and inhibition of acid secretion indicate that a ranitidine concentration of around 160 ng/ml is required for 50% inhibition of pentagastrin-stimulated secretion over a 2-hour period (15).

5. Adverse Effects (25)

Ranitidine appears to be relatively free of reported adverse effects, particularly in comparison with cimetidine. It has been reported to cause headache (2-3%), malaise, dizziness, constipation, nausea, abdominal pain, and skin rash (< 1%).

6. Dosage (15, 25)

The usual oral adult dose of ranitidine is 150 mg twice daily in the treatment of duodenal or benign gastric ulcer. Treatment should be continued until the ulcer has healed, or if endoscopic reassessment is not possible, for 4 to 8 weeks. In patients with very high gastric acid secretion or Zollinger-Ellison syndrome the starting dose is 150 mg three times daily and this may be increased, as necessary, to within the range 600 to 900 mg per day. Ranitidine 150 mg at night is used as maintenance treatment to prevent ulcer recurrence.

Ranitidine injection may be given where oral treatment is inappropriate. The usual adult IM or IV dosage is 50 mg every 6-8 hours.

Dosage should be decreased in patients with impaired renal function.

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