Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(7):70-78

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Ranitidine hydrochloride: An update on analytical, clinical and pharmacological aspects

Rakesh Pahwa[1*], Shilpa Sharma[1], Vipin Kumar[2] and Kanchan Kohli[3]

[1]*Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India*
[2]*Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Ajmer, India*
[3]*Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India*

ABSTRACT

Ranitidine hydrochloride has been extensively used in the treatment of diverse gastrointestinal disorders. This drug is a selective, competitive histamine H_2-receptor antagonist and established as a potent inhibitor of gastric acid secretion. Owing to its favourable efficacy and tolerability profiles, this drug has emerged as a first-line agent when suppression of gastric acid secretion is indicated. The current manuscript provides an updated account on the physicochemical aspects, analytical methodologies, clinical studies, pharmacokinetics, drug interactions and adverse effects of ranitidine hydrochloride.

Keywords: Ranitidine hydrochloride, H_2-receptor antagonist, Analytical methodologies, Clinical studies.

INTRODUCTION

H_2-receptor antagonists are the significant class of highly effective drugs for various acid-peptic diseases [1]. Acid secretion stimulated by gastrin or pentagastrin is inhibited by H_2-receptor antagonists. These antagonists are used to treat Zollinger-Ellison syndrome and peptic ulcer. Moreover, H_2-receptor antagonists are also useful in the prevention of stress ulceration and recurrence of gastric and duodenal ulcer [2-4]. Several H_2 antagonists are currently available in the market as cimetidine, ranitidine, famotidine, nizatidine etc [5].

Ranitidine is a histamine H_2-receptor antagonist which differs in chemical structure from both histamine and cimetidine [6]. Ranitidine is commonly employed in the management and treatment of acute duodenal ulcer disease, Zollinger-Ellison syndrome and systemic mastocytosis with gastric hypersecretion [6-9]. Ranitidine is the drug of choice in the treatment of the Zollinger-Ellison syndrome because of its increased potency and lesser effect on endocrine function compared to cimetidine [10]. This drug is a selective, competitive histamine H_2-receptor antagonist and is utilized in the short-term treatment of active duodenal ulcers and gastric hypersecretory conditions [11-12]. The action of ranitidine is selective since high concentrations of this drug do not affect β-adrenoreceptor, histamine H_1 and muscarinic receptor mediated responses [13]. Ranitidine is more potent than cimetidine in inhibition of gastric acid secretion and also lacks cimetidine's anti-androgenic and hepatic microsomal enzyme inhibiting effects [14-15]. In addition, ranitidine is a specific, long-acting antagonist that is indicated for gastroduodenal ulcer, gastroesophageal reflux and hypersecretory states [16]. It is effective by both parenteral and oral routes of administration [17-18].

Ranitidine has also been used safely in obstetric patients during labour, in children, in elderly, and in patients with renal impairment when given in appropriate dosages. The drug is very well tolerated and is associated with rare serious adverse reactions or clinically significant drug interactions. Due to its favourable efficacy and tolerability profiles, ranitidine has considered as a first-line agent when suppression of gastric acid secretion is indicated [19].

Physicochemical aspects

Chemically, ranitidine hydrochloride is having a furan ring structure [1, 20-21]. Its IUPAC name is N-[2-[[[5-[(dimethylamino) methyl]-2-furanyl] methyl] thio] ethyl]-N'-methyl-2-nitro-1, 1-ethene diamine hydrochloride [22-25]. Its empirical formula is $C_{13}H_{22}N_4O_3S.HCl$. It is a white or pale yellow and crystalline powder. It exhibits polymorphism. It is freely soluble in water, sparingly soluble or slightly soluble in dehydrated alcohol and very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5-6.0 [26]. The chemical structure of ranitidine hydrochloride is depicted in Figure 1.

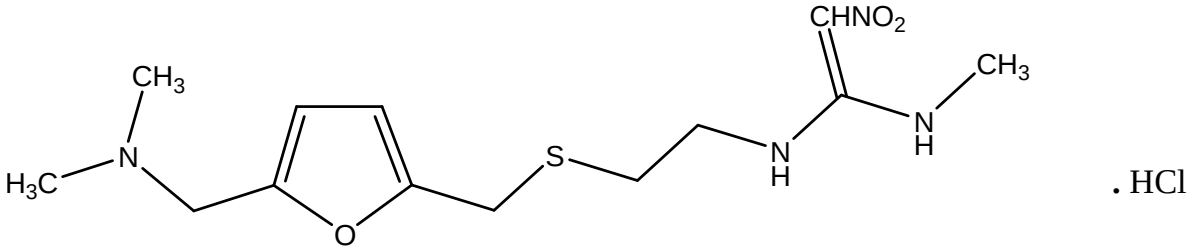

Fig 1: Structure of ranitidine hydrochloride

Mode of action

H_2-receptor antagonists exhibit competitive inhibition at the parietal cell H_2 receptor, and suppress basal and meal-stimulated acid secretion. H_2-receptor antagonists inhibit acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells. [24, 27-28].

H_2 antagonists reduce acid secretion stimulated by histamine as well as by gastrin and cholinomimetic agents through two mechanisms. Firstly, histamine released from enterochromaffin-like (ECL) cells by gastrin or vagal stimulation is blocked from binding to the parietal cell H_2 receptor. Secondly, direct stimulation of the parietal cell by gastrin or acetylcholine results in diminished acid secretion in the presence of H_2 receptor blockade [27].

The most prominent effects of H_2 receptor antagonist are on basal acid secretion and less profound but still significant is suppression of stimulated acid production. These agents thus are particular effective in suppressing nocturnal acid secretion, which reflects mainly basal parietal cell activity [4, 29].

Analytical methodologies

Various analytical studies have been carried out for the detection of ranitidine hydrochloride in pharmaceutical dosage forms and biological fluids. Some important analytical procedures reported in recent scientific literature are discussed in the following section:

Pratiwi D *et al* performed quantitative analysis of polymorphic mixture of ranitidine hydrochloride by Raman spectroscopy and principal component analysis (PCA). Study demonstrated that PCA of Raman spectroscopic data provides a sensitive method for the quantitative analysis of polymorphic impurities of drug in commercial tablets with a quantitation limit of less than 2% [30]. Taylor LS *et al* also employed Raman spectroscopy to evaluate solid state forms of active substance present in tablets and capsules [31]. Pedrouzo M *et al* described method for simultaneous determination of macrolides, sulfonamides, ranitidine and other pharmaceuticals in water samples by solid-phase extraction and liquid chromatography-electrospray ionization/mass spectrometry (LC-ESI)/MS. High concentration of ranitidine was found in sewage water with a maximum value of 0.24 microg/L [32]. Mirmehrabi M *et al* investigated solubility, dissolution rate and phase transition studies of ranitidine hydrochloride tautomeric forms [33].

Nozal MJ *et al* described high performance liquid chromatography (HPLC) method for determination of ranitidine hydrochloride residues on various surfaces employed in the manufacture of pharmaceuticals. The method was validated over a concentration range of 20-10000 ng/mL and had a detection limit of 2 ng/mL [34]. Vandenberghe HM *et al* described simple and rapid micro method for the high pressure liquid chromatographic analysis of ranitidine and N-[2[[[5-[(dimethylamino)-methyl]-2-furanyl] methyl]thio]-ethyl-N'-methyl-2-nitro-1,1-ethenediamine in serum or plasma. The percentage analytical recovery of ranitidine and internal standard was 99% and 81% respectively [35]. Sahoo BK *et al* developed and validated a simple, rapid and specific bioanalytical procedure for the quantification of ranitidine hydrochloride in human plasma by high performance liquid chromatography with UV detection [36]. Novakovic J *et al* validated high performance thin layer chromatographic (HPTLC) method for trace analysis of two different generic drugs - the water soluble H_2-receptor antagonist ranitidine hydrochloride and the water-insoluble choleretic drug ursodeoxycholic acid. HPTLC was performed on silica plates by using toluene-methanol-diethylamine and n-heptane-ethyl acetate-glacial acetic acid as the mobile

phase [37].

Mitsana-Papazoglou A *et al* investigated dissolution studies of drug formulations using ion selective electrodes as sensors in an air-segmented continuous flow analyzer. In this study, flow through electrodes selective to chlorpromazine, amitriptyline, propantheline, cimetidine and ranitidine have been constructed and used for dissolution studies of 18 dosage forms using rotating basket apparatus [38]. Rosa SS *et al* developed and validated near infrared diffuse reflectance spectroscopy method for identification and quantification of ranitidine in pharmaceutical products [39]. Stepanova EV *et al* addressed the use of IR spectroscopy in the near-infrared range for analyzing ranitidine hydrochloride substances and tablets [40].

Narayana B *et al* described a simple and sensitive spectrophotometric method for the determination of ranitidine hydrochloride in pharmaceuticals. This method was based on the formation of coloured condensed product with p-dimethylaminobenzaldehyde followed by measurement of absorbance at 503 nm [41]. Sarfaraz S *et al* developed a method (under International Conference on Harmonization (ICH) Guidelines) for the validation of ranitidine in its formulation [42]. Mali AD *et al* developed simple, fast and reliable spectrophotometric methods for the determination of ranitidine in bulk and pharmaceutical dosage forms. It has been concluded that all the proposed methods have been extensively validated as per ICH guidelines. There was no significant difference between the performance of the proposed methods regarding the mean values and standard deviations. Developed methods were successfully applied to estimate the amount of ranitidine in pharmaceutical formulations [43]. Walash M *et al* presented two spectrophotometric procedures for the determination of two commonly used H_2-receptor antagonists, nizatidine (I) and ranitidine hydrochloride (II). The methods were based mainly on charge transfer complexation reaction of these drugs with either p-chloranilic acid or 2, 3 dichloro-5, 6-dicyanoquinone (DDQ). The resulted coloured products were quantified spectrophotometrically at 515 and 467 nm in chloranilic acid and DDQ methods respectively [44].

An indirect flow injection spectrophotometric procedure was developed by Luiz H *et* al for the determination of ranitidine in pharmaceutical formulations. The method was applied with success in the determination of ranitidine in several commercial formulations [45]. Tadav PF *et al* studied the crystalline structure of the ranitidine hydrochloride using Terahertz pulse spectroscopy and found that method has a wide range of applications in pharmaceutical science including formulation, high throughput screening and inspection in storage [46]. Kelly MA *et al* studied optimization, validation and application of a capillary electrophoresis method for the determination of ranitidine hydrochloride and its related substances. Data obtained clearly shows that the performance of an optimized capillary electrophoresis method can be equivalent in terms of sensitivity and precision to that of a high performance liquid chromatography method employed for a similar purpose and offers better selectivity against thin layer chromatography and high performance liquid chromatography [47].

A simple and sensitive kinetic spectrophotometric method was described for analysis of nizatidine (I) and ranitidine (II) by Hassan EM *et al*. The method involved the reaction of the drugs with alkaline potassium permanganate. The reaction was monitored spectrophotometrically by measuring the rate of change of absorbance of the resulting manganate species. The method was satisfactorily applied for direct analysis of pharmaceutical preparations containing I and II [48]. Sokol A *et al* proposed three spectrophotometric methods based on a spectral analysis for quantification of ranitidine hydrochloride in the presence of its decomposition product without isolation from the matrix. Proposed methods were applied for assay of ranitidine hydrochloride contents in its preparation and for investigation of kinetics of its reaction with hydrogen peroxide [49]. Ahamed AMK *et al* developed simple kinetic spectrophotometric method and a flow injection-activated chemiluminescence for the determination of ranitidine hydrochloride in pharmaceutical preparations. These methods were applied successfully to determine the content of ranitidine hydrochloride in pharmaceutical preparations with a recovery of 97-99% [50]. A simple X-ray powder diffractometric method was developed by Agatonovic-Kustrin S *et al* for the qualitative and quantitative assay of the two crystalline modifications of ranitidine hydrochloride. Results obtained by the artificial neutral networks (ANNs) have a smaller standard deviation and relative error and a better precision at lower concentrations [51].

Lau-Cam CA *et al* developed a rapid reversed phase high performance liquid chromatography assay method for ranitidine hydrochloride in dosage forms. Method also separated ranitidine from its related compound ranitidine S-oxide. Detector responses were linearly related to on column concentrations of ranitidine and ranitidine S-oxide in the ranges 0.035-9.000 µg and 0.005-0.320 µg, respectively [52]. A selective, specific and stability-indicating gradient reverse phase high performance liquid chromatographic method was developed by Sharma N *et al* for the determination of ranitidine in presence of its impurities, forced degradation products and placebo substances such as saccharide and parabens [53]. A simple, precise, accurate and rapid reverse phase high performance liquid chromatographic method was developed by Naresh M *et al* for simultaneous estimation of ranitidine and domperidone in bulk and pharmaceutical dosage form. Developed method was validated in accordance to ICH

guidelines [54].

The analysis by supercritical fluid chromatography (SFC) of ranitidine and its metabolite isolated from biological fluids was demonstrated by Smith MS *et al.* Studies revealed the potential of SFC for the analysis of drugs and their phase I metabolites [55]. A rapid and sensitive bioanalytical method based on liquid chromatography coupled with mass spectrometry detection with positive ion electrospray ionization was developed by Kumar SKR *et al* for the determination of ranitidine hydrochloride in human plasma using clarithromycin as the internal standard. The method provides good sensitivity and excellent precision and reproducibility relatively short term analysis [56].

Vinas P *et al* used reversed phase liquid chromatography for determination of ranitidine and its main metabolites, ranitidine N-oxide and ranitidine S-oxide in plasma and urine. Detection was carried out by a post-column fluorimetric derivatization based on the reaction of the drugs with sodium hypochloride giving rise to primary amines that reacted with o-phthalaldehyde and 2-mercaptoethanol to form highly fluorescent products. Chromatographic profiles obtained for plasma and urine samples showed no interference from endogenous compounds [57]. Ulu ST *et al* described a sensitive and rapid determination of ranitidine in human plasma by high performance liquid chromatography with fluorescence detection. The method was validated for system suitability, precision, accuracy, linearity, limit of detection, limit of quantification, recovery and robustness [58]. Mirmehrabi M *et al* characterized tautomeric forms of ranitidine hydrochloride by thermal analysis, solid-state NMR and X-ray. It was found that significant amounts of strongly polar solvents such as methanol and water would favour the production of Form 2; while anhydrous less polar or non-polar solvents will result in the production of Form 1 [59].

Amin AS *et al* described three simple, accurate and sensitive colorimetric methods (A, B and C) for the determination of ranitidine hydrochloride in bulk sample, in dosage forms and in the presence of its oxidative degradates. It has been observed that validity of the proposed methods can be tested by analyzing pure and dosage forms containing ranitidine hydrochloride [60]. Richter P *et al* described a polarographic method for the determination of ranitidine based on the reduction of the nitro group at a dropping-mercury electrode. The proposed method permits the drug to be determined, without any prior separation or extraction, in pharmaceutical formulations and urine at levels at which the unchanged drug is excreted [61]. Khan S *et al* utilized strong cation exchange resin to improve the physicochemical properties of ranitidine hydrochloride such as taste and bulk properties and to sustain dissolution rate. Batch method was used to prepare drug resin complexes. Drug loading was done under different processing conditions such as temperature, pH, drug resin ratio and drug concentration to get the optimum condition for resinates preparation [62]. Chieng N *et al* developed a reliable quantification procedure for mixture of three solid forms of ranitidine hydrochloride using X-ray powder diffraction and Raman spectroscopy combined with multivariate analysis. It has been found that Raman spectroscopy provided better partial least squares regression models than X-ray powder diffraction, allowing a more accurate quantification [63].

Gore AH *et al* proposed a novel method for the quantitative determination of ranitidine hydrochloride based on the fluorescence quenching of functionalized Cds quantum dots (QDs) by ranitidine hydrochloride in aqueous solution. The method is simple, rapid, specific and highly sensitive with precision. The method was satisfactorily applied to the direct determination of ranitidine hydrochloride in pharmaceutical formulations with no significant interference from excipients [64]. A simple, rapid, accurate, precise and reproducible conductimetric method was examined by Issa YM *et al*. The proposed method was sensitive as a small amount of phenylpropanolamine HCl, ranitidine HCl, hyoscyamine HBr and betaine HCl could be determined with a good accuracy and without interference from excipients such as starch and glucose [65].

Ozden T *et al* developed a rapid and specific proton magnetic resonance (PMR) spectroscopic method for determining ranitidine hydrochloride in tablets. 2-choloroacetophenon was used as the internal standard and DMSO-d_6 served as the proton magnetic resonance solvent. The method using commercial products provided comparable results to those obtained by the methods of UV spectroscopy and USP XXIII [66]. A simple analytical method for ranitidine quantification was developed by Araujo WR *et al* based on the electrocatalytic oxidation of ranitidine on a glassy carbon electrode modified by electrochemical deposition of ruthenium oxide hexacyanoferrate. The proposed method improved the analytical parameters obtained by other electroanalytical methods for the quantification of this drug, and it was employed for quantification of ranitidine in three commercial samples [67]. Trifkovic M *et al* used several solvents and studied their impact on the polymorphic generation of ranitidine hydrochloride by using two different recrystallization modes. The solid-state FTIR and UV spectrophotometer were used for characterization and quantification of two polymorphic forms of ranitidine hydrochloride. It was found that methanol concentration greater than 10 wt % at nucleation onset favored formation of Form 2 [68]. Guerrieri PP *et al* elucidated the synergistic influence of self-originating impurities and water vapor on the degradation kinetics of the histamine H_2 receptor antagonist, ranitidine hydrochloride. It was demonstrated that the presence of degradants dramatically reduces the stability of crystalline ranitidine hydrochloride in the presence of moisture via elimination of the

induction period observed in the solid-state degradation profile for the pure drug [69].

Clinical aspects

Ranitidine hydrochloride is used for the treatment of peptic ulcer. Various clinical studies on ranitidine have been summarized in the subsequent section:

Fedorowicz Z *et al* assessed the safety and effectiveness of H_2-receptor antagonist in the treatment of urticaria. The study involved 144 participants and it was concluded that combination of ranitidine with diphenhydramine was more effective at improving the resolution of urticaria than diphenhydramine administrated alone [70]. Nima S *et al* performed a single dose, randomized, open-label and 2-period crossover study on 20 healthy volunteers. They investigated the gastrokinetic activity of *Morinda citrifolia* aqueous fruit extract (AFE) in human subjects by examining the gastrointestinal absorption of ranitidine. It was concluded that AFE has a unique gastrokinetic activity in the enhancement of rate and extent of ranitidine absorption [71].

Hawwa AF *et al* characterized the population pharmacokinetics of ranitidine in critically ill-children. They also determined the influence of various clinical and demographic factors on its disposition [72]. Bashar FR *et al* performed double-blind randomized controlled trial over 120 traumatic patients. The patients were divided into two equal groups receiving either intermittent intravenous ranitidine or pantoprazole to prevent stress ulcers. The study resulted that ICU patients using pump inhibitors have a three-fold increased risk of developing ventilator associated pneumonia in comparison to H_2-blocker receivers [73]. Ranjbar F *et al* aimed to study the efficacy of ranitidine in attenuating or preventing olanazpine-induced weight gain. A parallel 2-arm clinical trial was done on 52 patients with schizophrenia, schizoaffective and schizophreniform disorders who received olanzapine for the first time. All these were first-episode admitted patients. They were randomly allocated to receive either ranitidine or placebo. The trend of body mass index was compared between groups over 16-week course of treatment [74]. Henry DA *et al* conducted paired studies of hepatic microsomal function in eight subjects to compare the effect of cimetidine and ranitidine on hepatic drug metabolism. Results suggested that ranitidine has an advantage over cimetidine by not inhibiting microsomal drug oxidative function [75].

Misra UK *et al* performed a randomized placebo controlled trial of ranitidine versus sucralfate in patients with spontaneous intracerebral haemorrage for prevention of gastric hemorrhage. It has been concluded that ranitidine and sucralfate do not seem to significantly prevent gastric hemorrhage [76]. Yin OQ *et al* proposed and evaluated a modified two-portion absorption model based on physiological and biopharmaceutical considerations to describe the double-peak concentration-time curve of ranitidine. The study was used to characterize the absorption phases and estimation of pharmacokinetic parameters for drugs with two absorption peaks [77]. Bowes MT *et al* carried out the investigation to explore whether a single 300 mg dose of ranitidine given orally 2-3 h before magnetic resonance cholangiopancreatography (MRCP) could reduce the signal from stomach and duodenum. A double-blind, placebo controlled, randomized, crossover trial was carried out on thirty five volunteers. The study concluded that oral ranitidine is a cheap and effective agent to decrease signal from upper gastrointestinal tract and to improve visibility of biliary tree [78].

Gardner JD *et al* studied the determination of the time of onset of action of ranitidine and famotidine on intra-gastric activity. It has been observed that when onset was determined for the group using statistical significance, which does not depend on arbitrary cut-off points, ranitidine 75 mg had an earlier onset of action than did famotidine 10 mg [79]. Berstad A *et al* studied a double-blind conditions over fifty patients with endoscopically verified duodenal ulcers which were treated with 100 mg of ranitidine hydrochloride or identical placebo tablets twice daily. Endoscopic examination after four weeks of treatment showed that the ulcer had healed in twenty three out of twenty five patients treated with ranitidine and in eleven out of twenty four patients with placebo. Moreover, no serious side effects of ranitidine were observed [80]. Mohammed R *et al* studied the treatment of 'cimetidine resistant' peptic ulcers by ranitidine hydrochloride. Twelve patients with endoscopically confirmed peptic ulcers which had failed to heal despite standard cimetidine therapy were treated with 300 mg ranitidine hydrochloride daily for 4 to 8 weeks. Ranitidine therapy resulted in complete symptomatic relief with endoscopically proven ulcer healing in six (50%) patients [81]. A randomized, double-blind, parallel, multi-clinic trial was conducted by Dammann HG *et al* to study the safety and efficacy of enprostil (35 µg twice daily) and ranitidine (150 mg twice daily) in the treatment of active gastric ulcer in ninety three outpatients (forty seven enprostil treated patients and forty six ranitidine). The two treatment groups were well matched for demographic characteristics. Study demonstrated that a prostaglandin E_2 analogue, enprostil, in a dose of 35 µg twice daily, is similar safe and effective as ranitidine in the treatment of active gastric ulcer [82].

Higuchi K *et al* investigated the effects of ranitidine compared with those of famotidine on the quality of gastric ulcer healing. They randomly assigned sixty nine consecutive patients with gastric ulcers to ranitidine (n = 34) or

famotidine (n = 35) for 12 weeks, with endoscopic assessment of the quality of gastric ulcer healing and histological assessment of gastric mucosa 12 weeks after the treatment started. It has been concluded that initial therapy with ranitidine significantly improved the quality of gastric ulcer healing and the histological scores of gastric mucosa compared with famotidine [83]. Collen MJ *et al* compared ranitidine and cimetidine for their abilities to control acid secretion on a short and long-term basis in 13 patients with gastric hypersecretory disorders. These studies showed that ranitidine can adequately inhibit acid secretion in patients with gastric hypersecretory disorders and also does not cause the antiandrogen side effects frequently seen with high doses of cimetidine, and is three fold more potent than cimetidine [84].

Pharmacokinetic aspects

Pharmacokinetics characteristics of ranitidine hydrochloride are described below:

Absorption

Ranitidine is readily absorbed from the gastrointestinal tract with peak concentration in plasma occurring about 2 to 3 h after oral administration [5, 26]. The oral bioavailability of ranitidine is about 50%. Drug is rapidly absorbed when administered via the oral route and absorption after oral administration is linear [27, 85, 86]. Ranitidine is highly water soluble and has pKa values of 8.2 and 2.7 [87]. The bioavailability of ranitidine is significantly lower when administered as a solution directly to the colon instead of stomach, jejunum, or ileum. Food in general has no effect on the rate and extent of absorption of drug [85]. Ranitidine is rapidly absorbed on intramuscular injection, resulting in peak plasma concentration occurring in about 15 minutes [26].

Distribution

The apparent volume of the distribution for terminal phase is about 1.16-1.87 L/kg. It is weakly bound, about 15% to plasma proteins [27, 85]. Ranitidine crosses the placental barrier and is distributed into breast milk [26].

Metabolism

A small proportion of ranitidine is metabolized in the liver [5, 86]. The hepatic metabolism of the drug results in production of metabolites i.e. N-oxide, the S-oxide and desmethylranitidine; the proportions of the various metabolites varies from one species to another and is also affected by the mode of administration. In man, N-oxide is the major metabolite but accounts for only about 4-6% of a dose.

After intravenous administration, the recovery of unchanged ranitidine plus its three major metabolites does not amount to 100%. This has been elucidated as revealing biliary excretion of some metabolites of ranitidine. In most studies, reduced bioavailability of ranitidine and reduced recovery of unchanged ranitidine in the urine after oral administration signify high presystemic hepatic metabolism [26, 27, 86, 88].

Excretion

About 30% of an oral dose and 70% of an intravenous dose is excreted unchanged in the urine in 24 h, primarily by active tubular secretion. Of orally administrated ranitidine, 26% is excreted through the faeces also. Elimination half life is about 2 to 3 h and is increased in renal impairment. In most studies, the elimination half-life after oral administration has been longer than that after intravenous administration [87]. Renal clearance values amount to some 70% to 80% of total clearance, indicating that renal excretion is the major route of elimination of unchanged ranitidine after intravenous administration [26, 27, 86, 88]. Various pharmacokinetic properties of ranitidine hydrochloride are summarized in Table 1.

Table 1: Pharmacokinetic profile of ranitidine hydrochloride

Parameters	Extent/Value
Oral bioavailability	About 50%
Bound in plasma proteins	About 15%
Metabolites	N-oxide, S-oxide, Desmethylranitidine
Elimination half-life	About 2 to 3 h
Excretion	Primarily by active tubular secretion

Drug interactions

The pharmacokinetic interaction occurs when the absorption, clearance or rarely, the distribution of one drug is modified by another. Several drug interactions of ranitidine hydrochloride (Table 2) are described in the subsequent section [89-98].

Table 2: Drug interactions of ranitidine hydrochloride

Interactant	Interaction
Metoprolol	Increases mean peak plasma concentration
Procainamide	Reduction in renal clearance
Warfarin	Decreases clearance
Nifedipine	Increases the plasma area under curve
Midazolam	Increases bioavailability
Chloromethiazole	Prolonged the elimination half-life
Ketoconazole	Decrease in bioavailability
Glipizide	Increases the plasma area under curve

Adverse effects

Ranitidine hydrochloride is one of the most extensively studied and widely used drugs of all time. This has provided an excellent opportunity to define its safety profile. However, the use of this drug may associated with some side effects which include headache, skin rashes, tiredness, constipation, nausea, diarrhoea, bradycardia, hypersensitivity, contact dermatitis, urticaria etc. A case of severe anaphylaxis to ranitidine is also reported [6, 9, 13, 99-108]. In addition, a case of ranitidine-induced photosensitivity is also reported [109]. Ranitidine, when given in conventional doses, can cause adverse central nervous system reactions as lethargy, confusion, somnolence and disorientation particularly in older patients who have substantial renal function impairment [110].

CONCLUSION

Although ranitidine hydrochloride is a relatively old drug, yet it is still a very effective and clinically important antiulcer agent. Significant pharmacological interventions, pharmacokinetic aspects and current analytical methodologies for its determination or identification in various formulations and biological fluids have been described. This drug has emerged as a promising, time tested and efficacious agent in the treatment of various gastrointestinal disorders. It is emphasized that further scientific and technological advancements in pharmacology and analytical techniques are still needed to precisely control the therapeutic and quality attributes of this potent medicinal agent.

Acknowledgement

Prof. A. C. Rana, Dean and Director, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India, is duly acknowledged for providing necessary facilities.

REFERENCES

[1] KD Tripathi. Essential of Medical Pharmacology, 6th Edition, Jaypee Medical Publisher, New Delhi, **2010;** 628-630.
[2] JW Black. *Klini. Wochenschr*., **1976**, 54(19), 911-914.
[3] RJ Lipsy; B Fennerty; TC Fagan. *Arch. Intern. Med.*, **1990**, 150(4), 745-751.
[4] R Pahwa; Neeta; V Kumar; K Kohli. *Int. J. Pharm. Sci. Drug Res.*, **2010**, 2(2), 99-106.
[5] JG Hardman; Limbrid (Eds.) Goodman and Gilman's. The Pharmacological Basis of Therapeutics, 10th edition, McGraw-Hill Co., New York, **2001**, 999-1000.
[6] J Dawson; DA Richards; R Stables; GT Dixon; R Cockel. *J. Clin. Hosp. Pharm*., 1983, 8(1), 1-13.
[7] M Mitchard; A Harris; BM Mullinger. *Pharmacol. Ther*., **1987**, 32(3), 293-325.
[8] WB Strum. *JAMA*, **1983**, 250(14), 1894-1896.
[9] D Chopra; P Arora; S Khan; S Dwivedi. *Indian J. Pharmacol*., **2014**, 46(2), 234-236.
[10] CA Helman; LO Tin. *Pharmacother.*, **1983**, 3(4), 185-192.
[11] TS GaginellA; JH Bauman. *Drug Intell. Clin. Pharm.*, **1983**, 17(12), 873-885.
[12] JB Zeldis; LS Friedman; KJ Isselbacher. *N. Engl. J. Med*., **1983**, 309(22), 1368-1373.
[13] MJ Daly; R Stables. *Agents Actions*, **1980**, 10(1-2), 190-191.
[14] K Florey. Analytical profile of drug substances. 10th edition, Academic Press, London, UK, **1986**; 15; 533-561.
[15] RN Brogden; AA Carmine; RC Heel; TM Speight; GS Avery. *Drugs*, **1982**, 24(4), 267-303.
[16] K Aouam; W Bouida; N Ben Fredj; A Chaabane; H Boubaker; R Boukef; NA Boughattas; S Nouira. *J. Clin. Pharm. Ther*., **2011**, 37(4), 494-496.
[17] EP Woodings; GT Dixon; C Harrison; P Carey; DA Richards. *Gut*, **1980**, 21(3), 187-191.
[18] JJ Mcneil; GW Mihaly; A Anderson; AW Marshall; RA Smallwood; WJ Louis. *Br. J. Clin. Pharmacol.*, **1981**, 12, 411-415.
[19] SM Grant; HD Langtry; RN Brogden. *Drugs*, **1987**, 37(6), 801-807.
[20] MJ Daly; JM Humphray; R Stables. *Br. J. Pharmacol.*, **1981**, 72, 49-54.
[21] RE Pounder. *Pharmacol. Ther.*, **1984**, 26(2), 221-234.

[22] T Ishida; Y In; M Inoue. *Acta Cryst.*, **1990**, 1893-1896.
[23] British Pharmacopoeia. The British Pharmacopoeia Commission, London, **2009**, 5168-5173.
[24] ST Ulu; MB Cakar. *Opt. Spectrosc.*, **2012**, 113(2), 126-130.
[25] Indian Pharmacopoeia. The Indian Pharmacopoeia Commission, Ghaziabad, **2007**, 1037-1038.
[26] SC Sweetman; Martindale. The Complete Drug Reference, 35th edition, Pharmaceutical Press, London, **2007**, 1590-1592.
[27] BG Katzung. Basic and Clinical Pharmacology, 9th edition, McGraw-Hill Companies, Singapore, **2004**, 1035-1036.
[28] Rang and Dale. Pharmacology, 5th edition, Churuchill Livingstone, India, **2003**, 369-370.
[29] HG Dammann; P Muller; H Kather; B Simon. *Res. Exp. Med.*, **1981**, 178(2), 151-154.
[30] D Pratiwi; JP Fawcett; KC Gordon; T Rades. *Eur. J. Pharm. Biopharm.*, **2002**, 54(3), 337-341.
[31] LS Taylor; FW Langkilde. *J. Pharm. Sci*., **2000**, 89(10), 1342-1353.
[32] M Pedrouzo; F Borrull; RM Marce; E Pocurull. *J. Sep. Sci*., **2008**, 31(12), 2182-2188.
[33] M Mirmehrabi; S Rohani; KS Murthy; B Radatus. *Int. J. Pharm.*, **2004**, 282(1-2), 73-85.
[34] MJ Nozal; JL Bernal; L Toribio; MT Martin; FJ Diez. *J. Chromatogr. A.*, **2001**, 919(1), 87-93.
[35] HM Vandenberghe; SM Macleod; WA Mahon; PA Lebert; SJ Soldin. *Ther. Drug Monit.*, **1980**, 2(4), 379-384.
[36] BK Sahoo; J Mukherjee; TP Pal. *Int. J. Pharm. Pharm. Sci.*, **2011**, 3(2), 34-38.
[37] J Novakovic. *J. AOAC Int.*, **2000**, 83(6), 1507-1516.
[38] A Mitsana-Papazoglou; TK Christopoulos; EP Diamandis; MA Koupparis. *J. Pharm. Sci.*, **1987**, 76(9), 724-730.
[39] SS Rosa; PA Barata; JM Martins; JC Menezes. *Talanta*, **2008**, 75(3), 725-733.
[40] EV Stepanova; AP Arzamastsev; AV Titova. *Pharm. Chem. J.*, **2009**, 43(7), 425-427.
[41] B Narayana; K Ashwini; DN Shetty; K Veena. *Eurasian J. Anal. Chem.*, **2010**, 5(1), 63-72.
[42] S Sarfaraz; VR Reddy. *J. Chem. Pharm. Res.*, **2014**, 6(3), 1228-1232.
[43] AD Mali. *Int. J. Anal. Pharm. Biomed. Sci.*, **2015**, 4(6), 7-16.
[44] M Walash; M Sharaf-El Din; M Metwalli; MR Shabana. *Arch. Pharm. Res.*, **2004**, 27(7), 720-726.
[45] H Luiz; CS Luiz; J Heberth; Orlando. *Curr. Anal. Chem.*, **2009**, 5(3), 213-218.
[46] PF Tadav; IV Bradley; DD Arnone; M Pepper. *J. Pharm. Sci.*, **2003**, 92(4), 831- 838.
[47] MA Kelly; KD Altria; C Grace; BJ Clark. *J. Chromatogr. A*, **1998**, 798(1-2), 297-306.
[48] EM Hassan; F Belal. *J. Pharm. Biomed. Anal.*, **2002**, 27(1-2), 31-38.
[49] A Sokol; J Karpiska; R Talecka; B Starczewska. *Acta Pol. Pharm.*, **2011**, 68(2), 169-177.
[50] AMK Ahamed; AI Khaleel; ST Amine. *Natl. J. Chem.*, **2006**, 24, 534-550.
[51] S Agatonovic-Kustrin; V Wu; T Rades; D Saville; IG Tucker. *Int. J. Pharm.*, **1999**, 184(1), 107-114.
[52] CA Lau-Cam; M Rahman; RW Roos. *J. Liq. Chromatogr.*, **1994**, 17(5), 1089-1104.
[53] N Sharma; SS Rao; NDA Kumar; PS Reddy; AM Reddy. *Sci. Pharm.*, **2011**, 79(2), 309-322.
[54] M Naresh; T Ganesh; A Biswal; GN Reddy. *Int. J. Chem. Natl. Sci.*, **2013**, 1(1), 25-28.
[55] MS Smith; J Oxford; MB Evans. *J. Chromatogr. A.*, **1994**, 683(2), 402-406.
[56] SKR Kumar; JSK Nagarajan; SN Meyyanathan. *Int. J. Pharm. Pharm. Sci.*, **2014**, 6(2), 482-485.
[57] P Vinas; N Campillo; C Lopez-Erroz; M Harnandez-Cordoba. *J. Chromatogr. B. Biomed. Sci. Appl.*, **1997**, 693(2), 443-449.
[58] ST Ulu; M Tuncel. *J. Chromatogr. Sci.*, **2012**, 50(4), 301–306.
[59] M Mirmehrabi; S Rohani; KSK Murthy; B Radatus. *J. Cryst. Growth*, **2004**, 260(3-4), 517-526.
[60] AS Amin; IS Ahmed; HA Dessouki; EA Gouda. *Spectrochim. Acta A Mol. Biomol. Spectrosc.*, **2003**, 59(4), 695-703.
[61] P Richter; M Toral; F Muiioz-Varga. *Analyst*, **1994**, 119(6), 1371-1374.
[62] S Khan; A Guha; PG Yeole; P Katariya. *Indian J. Pharm. Sci.*, **2007**, 69(5), 626-632.
[63] N Chieng; S Rehder; D Saville; T Rades; J Aaltonen. *J. Pharm. Biomed. Anal.*, **2009**, 49(1), 18-25.
[64] AH Gore; US Mote; SS Tele; PV Anbhule; MC Rath; SR Patil; GB Kolekar. *Analyst*, **2011**, 136(12), 2606-2612.
[65] YM Issa; AFA Youssef; AA Mutair. *IL Farmaco*, **2005**, 60(6), 541-546.
[66] T Ozden; A Ungormuş; A Tosun; S Ersan. *Spectrosc. Lett.*, **1997**, 30(5), 835-841.
[67] WR Araujo; TRL Paixao. *Electroanalysis*, **2011**, 23(11), 2549-2554.
[68] M Trifkovic; S Rohani. *Org. Process Res. Dev.*, **2007**, 11(1), 138-143.
[69] PP Guerrieri; DT Smith; LS Taylor. *Langmuir*, **2008**, 24(8), 3850-3856.
[70] Z Fedorowicz; EJ Van-Zuuren; N Hu. *Cochrane Database Syst. Rev.*, **2012**, 14(3), 1-36.
[71] S Nima; S Kasiwong; W Ridtitid; N Thaenmanee; S Mahattanadul. *J. Ethnopharmacol.*, **2012**, 142(2), 354-361.
[72] AF Hawwa; PM Westwood; PS Collier; JS Millership; S Yakkundi; G Thurley; MD Shields; AJ Nunn; HL Halliday; JC McElnay. *Br. J. Clin. Pharmacol.*, **2013**, 75(5), 1265-1276.
[73] FR Bashar; N Manuchehrian; M Mahmoudabadi; MR Hajiesmaeili; S Torabian. *Tanaffos*, **2013**, 12(2), 16-21.
[74] F Ranjbar; A Ghanepour; H Sadeghi-Bazargani; M Asadlo; A Alizade. *BioMed. Res. Int.*, **2013**, 1-6.

[75] DA Henry; IA Macdonald; G Kitchingman; GD Bell; MJS Langman. *Br. Med. J.*, **1980**, 281(6243), 775-777.
[76] UK Misra; J Kalita; S Pandey; SK Mandal; M Srivastava. *J. Neurol. Sci*., **2005**, 239(1), 5-10.
[77] QP Yin; B Tomlinson; HL Chow; SS Chow. *Clin. Pharmacokinet.*, **2003**, 42(2), 179-192.
[78] MT Bowes; DF Martin; A Melling; D Roberts; HU Laasch; S Sukumar; J Morris. *Clin. Radiol.*, **2007**, 62(1), 53-57.
[79] JD Gardner; AA Ciociola; M Robinson; RL Mcisaac. *Aliment. Pharmacol. Ther.*, **2002**, 16(7), 1317-1326.
[80] A Berstad; K Kett; E Aadland; E Carlsen; K Frislid; K Saxhaug; A Kruse-Jensem. *Scand. J. Gastroenterol.*, **1980**, 15(5), 637-639.
[81] R Mohammed; KG Mitchell; C Mackay. *Curr. Med. Res. Opin.*, **1981**, 7(8), 523-525.
[82] HG Dammann; W Huttemann; HD Kalek; HG Rohner; B Simon. *Am. J. Med.*, **1986**, 18(24), 80-84.
[83] K Higuchi; T Watanabe; K Tominaga; M Shiba; K Nakagawa; H Uno; K Kitada; H Satoh; S Chono; T Uchida; Y Fujiwara; T Arakawa. *Int. J. Clin. Pharmacol. Res.*, **2005**, 25(4), 187-194.
[84] MG Collen; JM Howard; KE McArthur; JP Raufman; MJ Cornelius; CA Ciarleglio; JD Gardner; RT Jensen. *Ann. Intern. Med.*, **1984**, 100(1), 52-58.
[85] H Kortejarvi; M Yliperttula; JB Dressmam; HE Junginer; KK Midha; VP Shah; DM Barend. *J. Pharm. Sci*., **2005**, 94(8), 1617-1625.
[86] Q Zhou; ZR Ruan; H Yuan; B Jiang; DH Xu. *World J. Gastroenterol.*, **2006**, 12(17), 2742-2748.
[87] CJC Roberts. *Clin. Pharmacokinet.*, **1984**, 9(3), 211-221.
[88] KM Koch; M Liu; IM Davis; S Shaw; Y. *Eur. J. Clin. Pharmacol.*, **1997**, 52(3), 229-264.
[89] W Kirch; H Hoensch; HD Janisch. *Clin. Pharmacokinet.*, **1984**, 9(6), 493-510.
[90] GI Adebayo. *Biopharm. Drug. Dispos.*, **1989**, 10(1), 77-85.
[91] U Kloyz; HK Kroemer. *Pharmacol. Ther.*, **1991**, 50(2), 233-244.
[92] Fee JP; Collier PS; Howard PJ; Dundee JW. *Clin. Pharmacol. Ther.*, **1987**, 41(1), 80-84.
[93] RT Kubacka; EJ Antal; RP Jhul. *Br. J. Clin. Pharmacol.*, **1987**, 23(6), 743-751.
[94] SC Piscitelli; TF Goss; JH Wilton; DJ D'Andrea; H Goldstein; JJ Schentag. *Antimicrob. Agents Chemother.*, **1991**, 35(9), 1765-1771.
[95] PV Desmond; ML Mashford; PJ Harman; BJ Morphett; KJ Breen; YM Wang. *Clin. Pharmacol. Ther.*, **1984**, 35(3), 338-341.
[96] N Markawa; K Nishina; K Mikawa; M Shiga; H Obara. *Br. J. Anaesth.*, **1998,** 80(1), 53-57.
[97] J Feely J; WCJ Collins; M Cullen; AH Eldebani; RS Macwalter; NR Peden; IH Stevenson. *Br. J. Clin. Pharmacol.*, **1993**, 35(3), 321-323.
[98] B Delhotal-Landes; B Flouvat; F Liote; L Abel; P Meyer; P Vinceneux; C Carbon. *Clin. Pharmacol. Ther.*, **1988**, 44(4), 442-452.
[99] L Beaugerie; N Patey; N Brousse. *Gut*, **1995**, 37(5), 708-711.
[100] R Herrmann; RG Shaw; DJ Fone. *Aust. New. Zeal. J. Med.*, **1990**, 20(3), 243-244.
[101] DC Khera; SL Smith; SF Slabic. *Am. J. Gastroenterol.*, **1988**, 83(3), 332-333.
[102] BK Khandheria. *JAMA*, **1984**, 83(3), 332-333.
[103] A Alomar; L Puig; L Vilaltella. *Contact Dermititis*, **1987**, 17(1), 54-55.
[104] M Picardo; B Santucci. *Contact Dermititis*, **1983**, 9(4), 327.
[105] KG Wormsley. *Drugs*, **1993**, 46(6), 976-985.
[106] KH Park; j Pai; DG Song; DW Sim; HJ Park; JH Lee; KY Jeong; CH Pan; I Shin, JW Park. *Clin. Exp. Allergy.*, **2016**, 46(4), 631-639.
[107] JG Mill; KM Koch; C Webster; MA Sirgo; K Fitzerald; JR Wood. *Aliment. Pharmacol. Ther.*, **1997**, 11(1), 129-137.
[108] C Foti; N Cassano; R Panebianco; GF Calogiuri; GA Vena. *Immunopharmacol. Immunotoxicol.*, **2009,** 31(3), 414-416.
[109] P Todd; P Norris; JLM Hawk; AWP Duvivier. *Clin. Exp. Dermatol.*, **1995**, 20(2), 146 - 148.
[110] PH Slugg; MT Hang; CE Pippenger. *Arch. Intern. Med.*, **1992**, 152(11), 2325-2329.