International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.11 No.02, pp 115-123, 2018

Cimetidine : A Review

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Abstract : Cimetidine has been extensively used in the treatment of diverse gastrointestinal disorders. This drug is a selective, competitive histamine H_2 receptor antagonist. An extensive survey of literature has been published that includes various analytical, pharmacokinetic, clinical, analytical aspects, drug interactions and adverse effects of the drug.
Keywords : cimetidine, gastrointestinal, analytical, pharmacokinetic, clinical, analytical, adverse effects.

Introduction

H_2blockers are a group of medicine that reduces the amount of acid produced by the cell in the lining of the stomach. They are also called histamine H_2 receptor antagonist or commonly called H_2 blocker [1.].These is the first class of highly effective drug for acid-peptic disease.[2]

There are four H_2 antagonists [3]

- CIMETIDINE
- FAMOTIDINE
- RANITIDINE
- NIZATIDINE

Acid secretion stimulated by gastrin or pentagastrin is inhibited by H_2-receptor antagonist. These antagonists are used to treat zollinger-ellison syndrome and peptic ulcer. Moreover H_2 receptor are also useful in the prevention of stress ulceration and recurrence of gastric and duodenal ulcer [4-6.].

H_2 receptor blockers are also frequently used to relive the symptoms of GERD (GASTRO-ESOPHAGEL REFLUX DISEASE). These medication are available over the counter and prescription. Doctor may also recommend H_2 receptor blocker for off-label use.[7]

Cimetidine was the first H_2 blocker to be introduced clinically and is described as the prototype [1]. The drug is a specific competitive antagonist H_2 receptor at the paritel cell [8]which inhibit the histamine-stimulated secretion of gastric acid and reduce pepsin output. Hence cimetidine has been widely used in condition where inhibition of gastric acid secretion may be beneficial such as heart burn associated with acid reflux duodenal and gastric ulcer, gastroesophagel reflux disease and hypersecretory syndromes such as the Zollinger-Ellison's.[9;10]

International Journal of ChemTech Research, 2018,11(02): 115-123.

DOI= http://dx.doi.org/10.20902/IJCTR.2018.110213

In addition the drug is currently being considered for alternative indication [11]. This drug has the ability to chelate metal ion in blood plasma and in different tissue [12] and it had previously been suggested that the main therapeutic action of cimetidine might be mediated by its interaction with essential metal ions.[13,14]

Physicochemical Aspects

Cimetidine , N-cyno-N^{I}-methyl-N^{II}-{2-[(4-methyl -5-imidazolyl)-methylthio]ethyl}guanidine is a well-known antagonist for H_2 receptor [15] . Its empirical formula is $C_{10}H_{16}N_6S$. Cimetidine like histamine is an imidazole derivative and is a very polar molecule. The side chain is structurally specific but it differs from that of histamine it being longer and formally unchanged at physiological pH [16].

- **Appearance and Solubility**

  Cimetidine is a colourless crystalline solid with melting point 141-142^{o} C. It is slightly soluble in water .Its aqueous solubility is 11.4mg/ml at 37^{o}C at a final pH of 9.3 [17] .The minimum solubility determined in the Ph range 1-8 at 30^{0}C in 6 mg/ml [18]

- **Partition Coefficient**

  The n-octanol / water partition coefficient (log P) of cimetidine was reported as 2.5 at 37^{o} C pH 9.2 [17,19]

- **pKa**

  Cimetidine is weakly basic with the pka value reported as 6.80 [17] and 6.93 [20] .It is thus present at least partly in ionized form in the upper GIT.

- **Salt and polymorphs**

  A hydrochloride salt of cimetidine existing of four polymorphs of cimetidine i.e A,B,C (anhydrous) and D (monohydrate) have been reported [15,21]. The polymorphic form was shown to affect the physicochemical properties, the bioavailability as well as the clinical efficacy of cimetidine.

Pharmacological Aspects

Mode of Action

H_2 –receptor antagonist exhibit competitive inhibition at the parietal cell H_2 receptor and suppress basal and meal stimulated acid secretion.H_2 receptor antagonist inhibits acid production by reversibly competing with histamine for binding to H_2 receptor on the basolateral membrane of parietal cell.[22]

H_2antagonist reduces acid secretion stimulated by histamine as well as by gastrin and cholinomimetic agent through two mechanisms. Firstly histamine released from enterochromoffin –like (ECL) cell 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 result in diminished acid secretion in the presence of H_2receptor blockade.[4]

The most prominent effect of H_2 receptor antagonist are on basal acid secretion. These agent thus are particularly effective in suppressing nocturnal acid secretion which reflect mainly basal parietal cell activity.[23]

Clinical aspects

Cimetidine are widely used in conditions in which it is profitable to suppress gastric acid secretion [2,3].Various clinical studies on cimetidine have been summarized in this section.

Tuskey and Peura(2013) studied the use of H_2 antagonist (cimetidine) in treating and preventing NSAID –induced mucosal damage.[24]

Pantziarka et al. (2014) performed a study to determine the anticancer activity of cimetidine and concluded that cimetidine is a very strong candidate for repurposing as an oncological treatment, particularly as a perioperative treatment for surgical resection of solid tumors in combination with existing standard

treatment.[25] The H_2 receptor antagonist cimetidine was first proposed as an anticancer agent in 1979 (Armitage and Sidner ,1979)[26]

M.N SATO et al.(1991)studied the immunomodulatory effect of cimetidine on the proliferative responses of splenocytes.[27].Cimetidine was suggested as an effective prophylactic treatment for PFAPA in 1992 by Feder[28]

Minocha et al. (1995) reported that cimetidine appears to have a role in the treatment of chronic idiopathic urticaria and some other type of urticaria when used in combination with various H_2 blocker [29] for symptomatic dermatographism, the combination of an antihistamine and H_2 antagonist such as chlorpheniramine and cimetidine, appears to be effective.[30] Cimetidine might also increase the latency time of heal induced urticarial.[31]

Sharma (1998) reported that molluscumcontagiosuma common illness in children caused by a pox virus has been treated with cimetidine[32] at a dose of 30-40 mg/kg. It has been used as a treatment for children [33] and adult[34]. **Chang** et al. (2006) studied the treatment of molluscumcontagiosum with high dose of cimetidine therapy.[35]

Various open-label studies have been published regarding the safety and efficacy of cimetidine in the treatment of common warts.[36-39].**Yilmaz**et al. (1996) conducted a randomized, placebo-controlled, double-blind trial to evaluate the efficacy of cimetidine therapy in patient with multiple warts[40]. **Fit** et al. (2007) studied the use of H_2 antagonist for the treatment of verruca vulgaris.[41]

Pireset al. (2013) reported that cimetidine can be a possible pharmacological alternative for the treatment of hypersexuality in children and adolescent with psychiatric disorders.[42]

Pharmacokinetic Aspects

Absorption

Cimetidine is adequately absorbed after oral administration. Its bioavailability is between 56-68% in healthy subjects and about 70% in patient with peptic ulcer disease in whom a much greater variation in absorption was observed.[19,43]

In the feed state the absorption of cimetidine is slightly delayed but the extent absorbed is not significantly different to that in the fasted state [44]. Cimetidine is slightly soluble in water and has pka value of 6.80[17]and 6.93 [20]. A bioavailability study in a patient with a massive bowel restriction demonstrated reduced absorption of cimetidine which was attributed to rapid transit of drug through the GIT tract[45]. Both the absorption and clearance of cimetidine are linear in the therapeutic range[19,46]. Using the everted d ring technique the uptake of cimetidine from the rat jejunum and colon was show to be linear in the range 0.005- 40 nM[47]. After oral administration in the fasted state cimetidine usually show erratic double peak or multiple peak phenomenon in plasma drug concentration-time profile[19,44,48]. The phenomenon has been described extensively and still under discussion.

Distribution

The volume of distribution of cimetidine whether expressed at a steady-state (vdss) or the area volume of distribution (vd_B) is approximately 0.8-1.39 w/kg[19, 46]. The value decreases with increasing age. It crosses placenta and reaches milk but penetration in brain is poor because of its hydrophilic nature [2]. The plasma protein binding of cimetidine is as low as 19%.[49]

Metabolism and Excretion

In human cimetidine has a circulating half life of disappearance of 123±12 min[50]. Cimetidine and its metabolism are eliminated predominantly via kidney [19]. .Peak blood level is absorbed orally and approximately 70% is excreted intact in the urine[50]. Fecal losses account for approximately 10% of cimetidine excretion[51]. Inactivation of cimetidine is primarily by hepatic conversion of side chain thioether moiety to the sulfoxide[52,53]. With respect to metabolism in the GIT tract the human jejuna perfusion study conducted by HUI et al.

(1994)demonstrated that cimetidine metabolite constituted 3% and 6% of the initial cimetidine concentration over 50cm of jejunum in two subjects[54].The pharmacokinetic profile of cimetidine has been shown in table 1

Analytical Method for Detection

Various analytical studies have been carried out for detection of cimetidine. Some imported analytical method reported in recent scientific literature and discussed in the following section

A selective sensitive and accurate high performance liquid chromatography method was developed ,validated and applied for the determination of cimetidine and ranitidine in plasma by **Zendelovska & Stafilov (**2003) [55]. HPLC method presented by **Jantratid** et al. (2007) involved a simplified sample preparation by protein precipitation with perchloric acid.[56]

Dong –sun et al. (1995)presented an analytical work saving online-column switching HPLC method with UV detection for clearup and analysis.[57]**Gomita**et al. 1989 established an HPLC method for micro determination of cimetidine in rat plasma.[58]**Betto** et al. 1991 developed an HPLC method with diode-array detector in order to assay cimetidine and its related impurities in pharmaceutical formulation.[59]

A rapid method for the simultaneous quantitation of the H_2 receptor antagonist drug cimetidine and ranitidine in human plasma by isocratic ion-pair reverse phase HPLC is described by **J. Boutagy**et al. (2006)[60]. The method involved a simple organic extraction step of the alkalinized plasma containing added internal standard followed by back extraction of the extract with dilute acetic acid and subsequent analysis of the aqueous acidic phase on a reverse phase (C18) column. The eluting solvent was acetonitrile-water (20:80v/v) containing 0.005 mole/liter octonesulphonic acid and was monitored at 229 nm. The run time for assay was 12.5 minutes, with a detection limit for cimetidine of 50 mg/ml.

Chih Ho et al.1999 described a high performance liquid chromatography procedure for the simultaneous determination of H_2 BLOCKER using two level full factorial design with three variable (volume of methanol, percentage of triethylamine and concentration of phosphate buffer) to select an acceptable mobile phase [61]. **De sowa** et al. (2014) described simple and rapid method for the determination of cimetidine in human plasma by high performance liquid chromatography – mass spectrometry (HPLC –MS / MS). This method has two major advantages, the short time required and low sample volume required.[62]

A validated, simple and sensitive fluorescence quenching method for determination of ranitidine, cimetidine and nizatidine in tablet and biological fluid was presented by C**hang** et al.(2011)[63]. This is the first single fluorescence method for the analysis of all H_2 antagonists.

Application of capillary zone electrophoresis to the quantitative estimation of cimetidine in rat urine was described by **Arrowood** et al. (1993)[64]. **Darwish** et al.(2008)described a simple, and sensitive spectrophotometric method of H_2 receptor antagonist by means of N- bromosuccinimide and P-aminophenol. This method was based on the reaction of these drugs with NBS and subsequent measuring of the excess N-bromosuccinimide by its reaction with P-aminophemol to give a violet colour product.[65]

Two sensitive and fast spectrophotometric method using batch and flow injection procedure for the determination of cemitidine are proposed by **Garcia** et al.(2003)[66] . A new simple titrimetric method was developed **Thimmaraju** et al.(2012)to estimate cimetidine in bulk and formulation .This method was found to be sensitive and in expensive do not require any sample processing step. In this method cemetidine was taken in against methanol and acetic acid titrated against 0.1N hydrochloric acid and 0.1N perchloric acid using methanol orange and crystal violet as indicator for utilization and non –aqueous titration[67]. **Kumar and Karpagaseluil**(1994) described a titrimetric method for the determination of cimetidine in pure form and doses form.[68]

Mitsana-papazoglou et al. (1987) described a liquid membrane and polyvinyl chloride matrix ion-selective electrode (IES) that responds to the cationic forms of cimetidine and ranitidine[69]. **Sanchez-Peren** et al. (1985) described a method which used the direct current polarographic behavior of cimetidine in strong acid to determine the cimetidine[70]

Dosage forms of cimetidine

- TABLET [71,72]
- SUSPENSION [73,74]
- GEL FORMULATION [75]

Drug Interaction

Drug-drug interactions are one of the commonest causes of medication error. Drug interaction refers to modification of response to one drug by another when they are administered simultaneously or in quick succession.[76] Drug interactions can be broadly divided into pharmacokinetic and pharmacodynamics interaction. The pharmacokinetic interaction occurs when the absorption, distribution, metabolism and elimination of one drug is modified by another.[2,4]**.**Several drug interaction of cimetidine are given below in Table 3

Adverse effects of cimetidine

Cimetidine is well tolerated by most patients. Adverse effect occurs in 5% cases. The use of this drug may be associated with some side effect which include :

- Headache, dizziness, bowel upset, dry mouth, rashes, constipation, diarrhea, insomnia, nausea, and muscle pain.[2]
- Cimetidine when give in high dose can cause impotence and temporary decrease in sperm count [2,88]
- Various CNS effect like confusion , psychomotor restlessness, hallucination and disorientation stupor and convulsion may reported [2,89]
- Cimetidine indusegynaecomussia[90]
- Thrombocytopenia recognize as one of the possible side effect of cimetidine therapy[91]
- Bradycardia, hypotension and even cardiac arrest has occurred with rapid bouls intravenous injection [92]

Conclusion

Cimetidine is a histamine H_2 receptor antagonist which is widely prescribed in gastric ulcer, duodena ulcer, gastroesophagel reflux and also in condition in which it is profitable to suppress gastric acid secretion .It is very effective and clinically important antiulcer agent . Significant physicochemical aspect, pharmacological aspect, pharmacokinetics aspect, analytical method for identification of cimetidine, drug-interaction and adverse effect have been described.

Table 1: Pharmacokinetic profile of Cimetidine

Parameters	Value
Bioavailability	56-68%
Plasma protein binding	19%
Elimination half life	2 hr.approx.
Pka	6.80, 6.93
Excretion	via kidney

Table 2: Brand of cimetidine available in market

Brand Name	Manufucture
Cimetidine (tab)	Cadila H
Cimetin (tab)	PCI
Tagamet HB (tab)	GlaxoSmithkline
Tagamet HB solution	GlaxoSmithkline
Ulciban (tab)	Torrent
Cimecare (cap)	Advacare

Table 3: Drug interactions of cimetidine

Drug	Interaction
Phenytoin	Cimetidine inhibits the hepatic microsomal oxidation system. Phenytoin also metabolized by the hepatic microsomal system.Cimetidine produced a significant increase in the plasma concentration of phenytoin.[77]
Theophyline	Decrease theophylline clearence[78]
Lidocaine	Decrease hepatic clearance [79,80]
Propanolol	Plasma level increases and reduce cleasence[81,82]
Warfarin	Reduce clearance [83]
Ketoconazole	Absorption is decreased [2]
Metronidazole	Plasma clearance of metronidazole decreased [84]
Nifedipine	Increases the AUC [85]
Quinidine	Increases the bioavailability [86,87]

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