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A Review on Novel H2 Receptor Antagonists-Lafutidine

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Abstract

This paper reviews the remarkable impact of H2-receptor antagonists Lafutidine in ulcer disease. The development and the scientific rationale of these agents are presented, and efficacy and safety aspects in the short- and long-term treatment of ulcer disease discussed. Review is also focused on Pharmacokinetic and Pharmacodynamics Parameters, analytical estimation and patents on formulation of different dosage form of Lafutidine.

Keywords: Lafutidine, H2 Receptor Antagonist, Ulcer.

1. Introduction

Lafutidine is new second generation histamine H2 receptor antagonist. In April 2000 it was approved for marketing in Japan for first the time.[1] In November 2009 approved for marketing in India. [2] Chemically, it is C22H29N3O4. IUPACE name is 2-[Furan-2-ylmethylsufinyl]-N-{4-[4-(piperidin-1-ylmethyl) pyridine – 2 -yl] oxy-(2Z)-but-2-en-1-yl} acetamide. The structure of Lafutidine is shown in figure 1. It occurs as a white to pale yellowish white crystalline powder. It is freely soluble in acetic acid, soluble in methanol, sparingly soluble in ethanol and practically insoluble in water.[3]Melting point of lafutidine is 96-99°C.[4]It has greater solubility in acidic medium whereas alkaline and neutral solubility is small.[1] It is determined that lafutidine degrades in neutral, alkaline and photolytic condition but remains stable in acidic condition.[5]

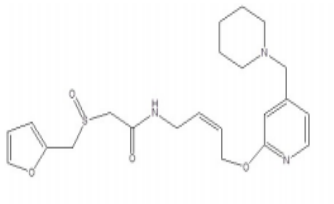

Figure 1: Structure of Lafutidine

It is used in the treatment of duodenal, gastric and stomal ulcers. It is also useful for gastric mucosal lesions and as Preanesthetic medication.[4] Normally 5-10 mg 2 times a day can considerably heal of gastric, duodenal ulcers, stomal ulcers and inhibit gastrin stimulated gastric acid secretion.[1] 10mg once a day use for Gastric mucosal lesions. As preanesthetic medication10mg lafutidine is orally administered twice, one before sleeping on the day before operation and one 2 hours before the introduction of anaesthetic on the day of operation.[4]

2. Clinical efficacy of Lafutidine

•Lafutidine not only decrease acid secretion but also strengthen the mucus barrier by stimulation of mucin synthesis.[6,7] It also enhances mucosal defense in rat the esophageal through inhibition of acid secretion and capsaicin-sensitive afferent neurons.[8,9] It is also effective in relieving the symptoms of heartburn-dominant uninvestigated dyspepsia.[10] It is also effective for the treatment of taxane-induced peripheral neuropathy in patients during treatment of gynecological malignancy.[11]

• Low dose aspirin and loxoprofen have a tendency to damage gastric mucosal layer. It was found that lafutidine significantly inhibit gastic mucosal damage produced by aspirin and loxoprofen at dose of 10mg. [12]

• Standard second line therapy for H. pylori is a combination of PPI with metronidazole– amoxicillin for 7 days. Lafutidine with metronidazole–amoxicillin as second-line therapy appears safe treatment similar to a PPI in H. pylori suppression in human volunteers.[13]

•Lafutidine–clarithromycin–amoxicillin therapy is also safe and effective as lansoprazolebased triple therapy for the eradication rate of H. pylori.[14]

• It is very safe and effective for reducing the intensity of oral burning sensation.[15]

• It is effective against ulcerative colitis induced by dextran sodium sulfate, through capsaicin sensitive efferent neurons and improving mucus secretion in colonic region.[16]

• It also reduces fasting and postprandial intra-gastric pH earlier than rabeprazole.[17]

3. Mechanism of action

•Lafutidine is a new histamine H2-receptor antagonist with both antigastric secretory and gastro-protective actions. [18]

• An antigastric secretory action of lafutidine is not only by blocking H2 receptors, but also through nitric oxide-mediated and inhibited distention-induced gastric acid secretion.[19] Nitric oxide has been reported to suppress gastric acid secretion by increasing cGMP in parietal cells.[19]

• Studies with certain antagonists or chemical differentiation techniques propose the gastroprotective actions of lafutidine to be mediated by capsaicin sensitive afferent nerves.[20] Capsaicin sensitive afferent nerves play an significant role in gastric mucosal defense mechanisms.[20] Capsaicin stimulates afferent nerves, enhances the release of calcitonin gene-related peptide (CGRP), which seems to be the principal neurotransmitter of spinal afferents in the rat stomach, exerting effects by a direct mechanism or indirectly through second messengers such as nitric oxide (NO).[20] Lafutidine also mimics endogenous effects of prostaglandins to augment the GMBF (gastric mucosal blood flow) and DAS (duodenal

HCO3 secretion), responses to acid or capsaicin, which likely by sensitizing CSN through an unknown site other than VR1.21 Lafutidine also protects the small intestine against ulceration via stimulation of capsaicin- sensitive sensory neurons; enhance endogenous NO produced by cNOS and increasing the mucus secretion.[21]

4. Pharmacokinetics and Pharmacodynamics

Parameter

Lafutidine is safe, well tolerated and shows liner pharmacokinetic up to 40mg. [22] The pharmacokinetics parameters mentioned in table 1 for lafutidine were determined by open label, randomized, two-way, two-period, two-treatment, single dose crossover bioequivalence study, under non fed condition for 10 mg dose.[23] Pharmacodynamics parameters for lafutidine were determined by a three way crossover design for 10mg dose and data for pharmacodynamic study are mentioned in table 2. [24]

Table 1: Pharmacokinetic parameter [23]

Parameter	Value
Cmax	265.15±49.84 ng/ml
AUC(0-t)	1033.13±298.74ng.h/ml
AUC(0-∞)	1047.61±301.22
tmax	0.95±0.24 h
K_{el}	0.44±0.19 h-1
t1/2	1.92±0.94 h

Table 2: Pharmacodynamics parameter [24].

Parameter	Value
kle	0.155±0.003 1/h
Ke0	0.316±0.012 1/h
Emax	3.686±0.222
EC50	40.68±2.70 ng/m

K_{le}- inter-compartmental transfer rate constant; ke0- equilibration rate constant; Emax- maximum effect; EC50- drug concentration needed for 50% of Emax

5. Analytical estimation of Lafutidine

There are different analytical methods available for estimation of Lafutidine in human plasma, dosage form etc., which is summarized in in Table 3.

Table 3: Analytical method for estimation of Lafutidine

Method	Procedure	Reference
Reverse phase high performance liquid chromatography	Method developed using Phenomenex Gemini c18 (4.6 x 250 mm, 5 µ) reverse phase column and Solid Phase Extraction technique. Chromatographic resolution of the lafutidine was achieved within 4.6 min by using mobile phase Methanol and 5 mM Di-Potassium Hydrogen Phosphate Buffer (pH 9.5) (80:20, v/v), flow rate was 1.0 mL/min at 216nm. Linear correlation observed in the range of 50-1000 ng/mL with correlation coefficient of 0.9996. Limit of Detection and Limit of Quantitation were 10 ng/mL and 30 ng/mL respectively, intra and inter-day deviations were lower than 3.92 % and 3.98 % respectively	**25**
UV spectrophotometric method	Lafutidine has maximum wavelength λmax 279nm in water and methanol (1:1). It obeys the Beer's law in the range of 10-50 µg/ml having line equation y=0.0100X+0.035 with r^2 0.999.	**26**
High-performance thin layer chromatography	Method developed for estimation of Lafutidine and domperidone. Chromatographic separation of the drugs was performed on aluminum plates precoated with silica gel 60 F254 as the stationary phase. Solvent system consisted of ethyl acetate: methanol : water (8:1:0.3) (v/v/v). The separated zones were evaluated at 223 nm. The two drugs were satisfactorily resolved with Rfvalues 0.34 ± 0.02 and 0.64 ± 0.02 for lafutidine and domperidone, respectively.	**27**
Liquid chromatography electrospray ionisation mass spectroscopy	Extraction form human plasma was done by liquid–liquid extraction with diethyl ether. For chromatographic separation stainless-steel column (C18 Shimpack5µm 150mm×2.0mm i.d. Shimadzu) at a flow rate of 0.2 ml/min by a gradient elution used. Detection was performed on a single quadrupole mass spectrometer by selected ion monitoring mode via electrospray ionization source. Linearity was established for the range of concentrations 1.0–400.0 ng/ml with a coefficient of determination of 0.9998. The intra- and inter-day precision (R.S.D.%) was lower than 10%and accuracy ranged from 85 to 115%. The lower limit of quantification was identifiable and reproducible at 0.5 ng/ml with 0.2 ml plasma.	**28**

6. Patents on lafutidine Dosage form

- Yang M patented method of preparation and liposomal solid preparation of lafutidine. Formulation consists of lafutidine with dipalmitoylphosphatidyl-glycerol, sodium deoxycholate and Span 80. Prepared formulations were excellent quality compared to conventional formulation.[29]
- Yue B patented solid medicament containing lafutidine. Invented formulation consists of solid dispersion prepared by polyethylene glycol 6000, polyethyleneglycol 4000,

mannitol and ElOO acrylic resin in one or several, in composition of 10 - 30%.[30]

•Li Q et al composition and preparation method for lafutidine. Formulation consists of 5- 20 % filler, 70-90% disintegrants, 0-15% lubricant, 0-5 % surfactant and 1-10 5 binders of coating component. The formulation was prepared by wet granulation technique.[31]

•Luo X et al invented method for preparing lafutidine from hydroxylamine hydrochloride. Patent comprises of chemical synthesis of lafutidine from hydroxylamine hydrochloride.[32]

•Lafutidine coated tablet and preparation method. The formulations consists of Lafutidine, lactose, microcrystalline cellulose, starch,sodiumcarboxymethyl starch, magnesium stearate and the composition of oralsolid preparations.[33]

• Cui et al invented gastric retention controlled release formulation for lafutidine. Formulation comprise of 5%-20% of the lafutidine, 10%-40% offramework materials, 10%-30% of assistant bleaching agents, 5%-15% offoaming agents, 5%-15% of filling agents and 0.5%-10% of lubricating agents. Invented formulation increases solubility, prolongs the action time from 2-3 hr to 5-6 hr on upper part of stomach and small intestine, promote absorption, enhances bioavailability and reduces frequency of administration.[1]

•Xiaoxin L et al patented method for preparation and lyophilized powder for injection of lafutidine. Freeze dried injection consists of lafutidine and mannitol in 1:10 to 100 ratio preferably in ratio of 1:20 to 50. It also contains sodium chloride and citrate.[34]

•Xiangwu M et al patented lafutidine tablet and its preparation method. Formulation contain 5-20 mg lafutidine, 10 to 50 percent of lactose, 5 to 30 percent of microcrystalline cellulose,5 to 45 %of starch, 2 to 15 g of sodium carboxy methyl starch, 0.1to 10 % of magnesium stearate, and 20 to 80 % of water act as a humectant.[35]

• Takeuchi K et al invented therapeutic agent comprising of lafutidine. They invented safer therapeutic agent for anti-inflammatory bowel disease, which is lafutidine, Its optical isomer and its salt.[36]

7. Safety Profile on Lafutidine

Lafutidine 10 mg was proven safe in acid peptic disorder patients. It shows slight adverse events like abdominal pain, diarrhoea, vomiting, bleching, excessive sleep, headache, fever and malaise.[37]

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