H2 RECEPTOR BLOCKERS (FAMOTIDINE)

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Introduction

Histamine-2 receptor antagonists (H2 blockers) are widely used in medicine for the suppression of gastric acid production. These drugs typically act by binding to histamine type 2 receptors on the basolateral (antiluminal) surface of gastric parietal cells, interfering with pathways of gastric acid production and secretion.[1]

Mechanisms of Action

1. Anti-viral activity

In a recent study, computational methods to predict structures of proteins encoded by the SARS-CoV-2 genome identified Famotidine as one of the drugs most likely to inhibit the 3-chymotrypsin-like protease (3CLpro) that processes proteins essential for viral replication.[2] Another in silico study revealed that famotidine can interact with the SARS-CoV2 main protease (3CLpro) as well as two other proteases involved in SARS-CoV2 replication, the viral PLpro and human host Tmprss2.[3]

2. Mast Cell Regulation

A preprint of a newer study proposes that unlike Cimetidine (and other H2 blockers), Famotidine acts as a partial agonist of arrestin recruitment. The drug molecule promotes internalization of the mast cell receptor and further non-canonical signaling once internalized through an arrestin-biased mechanism. The authors suggest that mast cell activation and histamine release may be central to lung pathology in patients with COVID-19 and the aforementioned mechanism contributes to the potential benefits of Famotidine therapy. This study has not yet been peer-reviewed.[4]

Clinical Studies

Currently ongoing in the United States is a multi-site, randomized, double-blind comparative clinical trial on the safety and efficacy of standard of care (SOC) plus Famotidine versus SOC plus placebo for the treatment of hospitalized patients with COVID 19. (Appendix 13)

A published retrospective cohort study done in New York, USA concluded that Famotidine use is associated with reduced risk of intubation or death in hospitalized COVID-19 patients. The study identified 1,620 hospitalized patients with COVID-19 including 84 (5.1%) who received famotidine within 24 hours of hospital admission. Three hundred forty (340) (21%) patients met the study composite outcome of death or intubation. Use of Famotidine was shown to be associated with reduced risk for death or intubation (adjusted hazard ratio (aHR)

0.42, 95% CI 0.21-0.85) and also with reduced risk for death alone (aHR 0.30, 95% CI 0.11-0.80). Proton pump inhibitors (PPIs), which also suppress gastric acid, were not associated with reduced risk for death or intubation.[5]

Another published case series done in New York, USA also suggests that oral famotidine is well tolerated and associated with improved patient-reported outcomes in non-hospitalised patients with COVID-19. Ten consecutive patients with COVID-19 who self-administered high-dose oral Famotidine were identified. Famotidine was well tolerated and all patients reported marked improvements of disease related symptoms after starting Famotidine. The researchers collected longitudinal severity scores of five symptoms (cough, shortness of breath, fatigue, headaches and anosmia) on a four-point ordinal scale modeled on performance status scoring. The combined symptom score improved significantly within 24 hours of starting Famotidine and peripheral oxygen saturation (n=2) and device recorded activity (n=1) increased.[6]

However, the findings of a preprint of a territory-wide retrospective cohort study (done in all COVID-19 patients reported in Hong Kong) do not support any association between famotidine and COVID- 19 severity. Of the 952 COVID-19 patients included in the study, 51 (5.4%) had severe disease as defined. Twenty three (2.4%) and four (0.4%) patients were given Famotidine and PPIs, respectively. There was no significant association between severe COVID-19 disease and use of famotidine (aOR: 1.34, 95% CI:0.24–6.06; p=0.72) or PPIs (aOR:0.75, 95% CI:0.07– 6.00; p=0.80). [7]

Recommended Dose

The proposed daily dose of Famotidine in the ongoing clinical trial for hospitalized patients with COVID-19 is 360 mg/day IV (120mg IV q8) for a maximum of 14 days.

The daily oral dose of Famotidine reported in the published case series on non-hospitalised patients with COVID-19 was 60 to 240 mg PO for a median of 11 days (range: 5-21 days).[6]

Adverse Effects

Since its introduction in 1985, Famotidine has been proven to be well tolerated in patients taking the drug for acid-related disorders and has a good safety profile.[8] Common side effects are headache, dizziness, diarrhea or constipation. Famotidine may contribute to QT prolongation particularly when used with other QT-elongating drugs, or in people with poor kidney function.[9]

Conclusion

Famotidine may have beneficial effects in the treatment of patients with COVID-19; however, with conflicting results in currently available literature, more studies are needed to verify its effectiveness, efficacy and safety.

REFERENCES:

1. Wallace JL, Sharkey KA. Pharmacotherapy of gastric acidity, peptic ulcers, and gastroesophageal reflux disease. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 11093-22.
2. Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods [published online ahead of print, 2020 Feb 27]. Acta Pharm Sin B. 2020;10(5):766-788. doi:10.1016/j.apsb.2020.02.008
3. Ortega JT, Serrano ML, Jastrzebska B. Class A G Protein-Coupled Receptor Antagonist Famotidine as a Therapeutic Alternative Against SARS-CoV2: An In Silico Analysis. Biomolecules. 2020;10(6):954. Published 2020 Jun 24. doi:10.3390/biom10060954
4. Malone RW, Tisdall P, Fremont-Smith P, et al. COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms. Preprint. *Res Sq*. 2020;rs.3.rs-30934. Published 2020 Jun 22. doi:10.21203/rs.3.rs-30934/v2
5. Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study [published online ahead of print, 2020 May 22]. Gastroenterology. 2020;S0016-5085(20)34706-5. doi:10.1053/j.gastro.2020.05.053
6. Janowitz T, Gablenz E, Pattinson D, et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series [published online ahead of print, 2020 Jun 4]. Gut. 2020;gutjnl-2020-321852. doi:10.1136/gutjnl-2020-321852
7. Cheung KS, Hung IF, Leung WK, Association between famotidine use and COVID-19 severity in Hong Kong: a territory-wide study, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.05.098 .
8. Howden CW, Tytgat GN. The tolerability and safety profile of famotidine. Clin Ther. 1996;18(1):36-35. doi:10.1016/s0149-2918(96)80177-9
9. Lee KW, Kayser SR, Hongo RH, Tseng ZH, Scheinman MM. Famotidine and long QT syndrome. Am J Cardiol. 2004;93(10):1325-1327.doi:10.1016/j.amjcard.2004.02.025