
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Of the 952 patients with COVID-19, 51 (5.4%) had severe disease as defined. Twenty-three (2.4%) and 4 (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; $P = .72$) or PPIs (aOR 0.75; 95% CI, 0.07–6.00; $P = .80$). Leucocyte count $>11 \times 10^9$/L (aOR 5.83; 95% CI, 1.43–2.12; $P = .010$) and lactate dehydrogenase >280 U/L (aOR 3.49; 95% CI, 1.52–7.97; $P = .003$) were independent laboratory parameters associated with severe COVID-19.

Hence, our findings did not support any association between famotidine and COVID-19 severity. Apart from difference in the various statistical adjustments including concurrent medication and laboratory parameters, we speculate that indication or selection bias may also confound the previous positive association, as a clinician's choice of famotidine over PPIs may be influenced by a patient's presentation, particularly on stress ulcer prophylaxis.[6] Because of the discrepant outcomes of the role of famotidine on COVID-19 severity, randomized trials are therefore needed to clarify the uncertain role of famotidine.

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**Conflicts of interest**
The authors disclose no conflicts.

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# What Underlies the Benefit of Famotidine Formulations Used During COVID-19?

Dear Editors:

This letter is in reference to the study by Freedberg et al[1] recently published in *Gastroenterology*. This retrospective analysis of an inpatient cohort admitted to 2 hospitals in New York found that patients with coronavirus disease 2019 (COVID-19) who were treated with famotidine exhibited a lower risk of death or mechanical ventilation as composite outcomes over a 30-day period. The study was based on computational modelling, which proposed famotidine might inhibit viral replication through direct interaction with the 3-chymotrypsin-like protease,[2] and was also preceded by a small, short-term follow-up, outpatient study suggesting that famotidine use was associated with symptomatic improvement.[3] However, the current study published in *Gastroenterology* provides additional value because the previous cohort was much smaller in number, included patients without a proven COVID-19 diagnosis, and lacked a control group.

The current study by Freedberg et al[1] brings a few questions to mind, which we hope the authors can answer. In the conclusions, the authors stated, "The study was premised on the assumption that use of famotidine represented a continuation of home use." In the Results section, they also say, "Home use of famotidine was documented on admission medication reconciliation in 15% of those who used famotidine while hospitalized." These points bring up a few questions.

1. Does this indicate that the remaining 85% patients given famotidine during hospitalization were using over the counter formulations at home which were not prescribed by a physician?
2. Were these formulations continued in-patient?
3. What were the formulations of famotidine used by the hospital pharmacies?
4. Did some included patients receive concomitant treatment with antacids, particularly calcium-containing compounds?
5. It is also mentioned that 28% hospitalized COVID-19 patients received famotidine intravenously. Was there a difference in outcomes between the intravenously treated group and the orally treated group?

We ask since popular over the counter famotidine formulations such as Pepcid Complete commonly contain 800 mg calcium carbonate per 10 mg famotidine. The answers to these questions are pathophysiologically relevant as we have recently published a report in your journal,[4] suggesting that the hypocalcemia commonly seen in severe COVID-19 disease is prognostically and mechanistically relevant to disease outcomes. We proposed that calcium supplementation early in the disease can, by interacting with fatty acids, decrease the lipotoxicity, which may exacerbate the disease and result in organ failure.

Using in silico molecular docking screens, famotidine has been characterized as potentially being able to bind papain-like protease (PLpro) and 3 chymotrypsin-like protease (Mpro) of SARS-CoV-2.[2,5] To explore this notion further, we downloaded crystal structures of PLpro and Mpro from RCSB.org (PDB IDs 6WX4 and 6LU7, respectively) and imported these to Schrodinger Maestro. The structures were prepared for docking, and famotidine was docked to both

proteases using the XP docking protocol. Famotidine was found to dock to PLpro with a GlideScore of −6.86 kcal/mol and to Mpro with a GlideScore of −4.05 kcal/mol. This finding represents a weak, nonspecific binding of famotidine to both PLpro and Mpro, and is in contradiction to previous molecular docking studies. Recently, in vitro experiments have shown that famotidine does not inhibit PLpro or Mpro, and it does not directly inhibit SARS-CoV-2 infection,[6,7] supporting our molecular docking data that famotidine does not bind to either protease. It has been hypothesized that famotidine could indirectly treat COVID-19 through antagonism or inverse agonism of histamine signaling as a result of binding to the H2 receptor,[6] but this hypothesis has yet to be rigorously tested.

Although the results of the randomized clinical trial on the benefits of intravenous famotidine in treating COVID-19 (NCT04370262) are excitedly awaited; the clues gained by the studies published in both *Gastroenterology*[1,4] and *Gut*,[3] give hope that COVID-19 could be combated by delving deeper into, and understanding the mechanistic basis of what was observed.

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**Reply.** Singh et al[1] are interested in the formulation of famotidine received by patients in our study and whether there was concurrent antacid use. In our retrospective study,[2] 15% of patients who received famotidine during hospitalization for Coronavirus Disease 2019 (COVID-19) had home use of famotidine documented on the electronic medication reconciliation that must be performed at the time of hospital admission (compared with 1% of patients who did not receive famotidine during hospitalization for COVID-19, $P < .01$). Accuracy of medication reconciliation can be poor, and this may have been especially true for over-the-counter medications, such as famotidine, during the peak of the pandemic. Manually reviewing charts, 55% of patients who received famotidine during hospitalization for COVID-19 had either documentation of gastroesophageal reflux disease or documentation of famotidine use in the hospital admission note. Although this leaves room for uncertainty, we believe the most likely explanation for receipt of famotidine during hospitalization was continuation of home use of famotidine.

Regarding dose and formulation, the median dose of famotidine received during hospitalization was 136 mg (interquartile range 63–233) over a median of 5.8 days. The famotidine in our study was predominantly manufactured by Major Pharmaceuticals (oral) and West-Ward Pharmaceuticals (intravenous). Neither of these manufacturers was involved in the study. Regarding mode of administration, there were only 84 patients who received famotidine, including some who received both oral and intravenous formulations, so there is insufficient power to compare clinical outcomes based on mode of administration of famotidine. We could not determine from the medical records whether outpatient famotidine formulations included calcium carbonate; concomitant use of antacids during hospitalization was not assessed, but is rare at our institution.

Cheung et al[3] present cross-sectional data related to famotidine exposure and severe COVID-19. The temporal relationship between famotidine exposure and outcomes in their study is unclear (ie, it is unclear whether famotidine administration preceded or followed the clinical outcomes). Several retrospective studies show relationships between famotidine and outcomes in COVID-19[4–6] and several do not.[3,7,8] Additional retrospective (or cross-sectional) studies are unlikely to produce definitive answers for this question. Like Cheung et al[3] and like Singh et al,[1] we eagerly await the results of the ongoing randomized controlled trial testing famotidine in hospitalized patients with COVID-19 (NCT04370262).

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