Peer Review File

Article information: https://dx.doi.org/10.21037/apm-23-311

Reviewer A

Line 43 should be synergistically
Done

I do not know if I have to add something to the subsequent comments. I do not think so (ranitidine and similar drugs have been removed from the market in many countries)…..:
• *From the Currow paper, what is not comprehended by Dr. Currow and the authors is that ranitidine uniquely releases somatostatin from the gastric wall. This is explained in the Davis paper and missed by the author and not mentioned by the strategy in the group. Such a randomized trial was a comparison of endogenous somatostatin versus exogenous octreotide plus endogenous somatostatin, which of course, would be comparing "apples and apples".*
No, Currow's study was a comparison between octreotide and placebo. Davis' ss paper is ref.11. However, given the case report, physiopathology and presumed mechanism were not the focus

"Ranitidine is a unique H2 receptor (histamine receptor) Blocker, which is distinctly different in regard to pharmacodynamics than other H2 agents such as famotidine and cimetidine.
Ranitidine similar to other H2 receptor blockers reduces gastric acidity and secretions [52]. However, in addition, ranitidine protects the gastric mucosa independent of its influence on gastric acid secretion and inhibits neutrophil activation
thus reducing inflammation [53]. Ranitidine increases the release of calcitonin gene-related peptide (CGRP) which within the stomach reduces acid secretion and gastric motility and stimulates blood flow [54–56]. The release of CGRP from the gastric mucosa is unique to ranitidine and does not occur with famotidine or cimetidine [57]. Ranitidine also uniquely increases the release of substance P which regulates gastric mucosal blood flow and increases gastric emptying [57]. Ranitidine unlike famotidine or cimetidine, has anti-cholinesterase activity yes, which may be the mechanism by which CGRP is increased [58, 59]. What may be important, particularly in the area of MBO management is that ranitidine increases the secretion and expression of somatostatin from and within the gastric mucosa [30]. The increase in CGRP caused by ranitidine increases the release of somatostatin from antral D cells.
Famotidine does not increase CGRP or yes somatostatin levels [60–66]. Therefore, the administration of ranitidine with subsequent increases in local and circulating somatostatin is likely to be one of the reasons why ranitidine is beneficial."
Itoh H (2006) Clinicopharmacological study of gastrointestinal drugs from the viewpoint of postmarketing development.1
Yakugaku Zasshi. 126(9):767–778 now we they need it fact that is what he told me this

morning.

• *Line 63 should be seventies*
Done
• *Line 66 "he got positive to COVID-19" is better described as he was infected with COVID-19*
Done
• *Line 83 should be hemicolectomy*
Done
• *Line 84 I am not sure what vicerolisis means. Is it lysis of adhesions or debulking surgery*
Done
• *Line 85 should be duodenectomy*
No, it is jejunectomy
• *Line 89 should be gastrostasis*
done
• *Line 92 should be hyponatremia*
done
• *Line 93 octreotide should not be capitalized*
It is at start of a sentence….
• *The first patient received an anti-muscarinic with metoclopramide which does not make sense since acetylcholine receptors are necessary for metoclopramide prokinesis.*
Buscopan and metoclopramide have been used for years for first line MBO treatment.

• *It may be that providing a prokinetic agent rather than octreotide may have led to the improvement. This ache that is what he told me is by speculation but is an alternative explanation.*
It is the combination of drugs with different mechanisms that provide a synergic effect.

• *Octreotide may work by inhibiting vasoactive intestinal peptides that may cause colic. Octreotide because of its stimulatory effects on phase III MMC activity as well as its known inhibitory effect on small bowel secretions.2*
Clinically I never observed this effect with hundreds of patients treated with octreotide (it would the same with the extrapiramidal effects of metoclopramide). The possible adverse effects should not deter the use.

1. Davis M, Hui D, Davies A, et al. Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update. Support Care Cancer. 2021;29(12):8089-8096.
2. Edmunds MC, Chen JD, Soykan I, Lin Z, McCallum RW. Effect of octreotide on gastric and small bowel motility in patients with gastroparesis. Aliment Pharmacol Ther. 1998;12(2):167-174.

Reviewer B

Overall, the article must be completely proofread by a native English speaker. For example, line 16 "that have never described" the verb "been" is missing, line 40 "there is typical cluster of symptoms", line 43 "synergically" is misspelled, line 83 "hémicolectomy" is misspelled, line 85 "digiunectomy" does not exist and so on...
For both cases, the authors reports that the patient had no stool for weeks. However, they do not report the passing of gas which would be highly important to make sure that we do not treat a partial bowel obstruction. Additonally, there is no evidence that the reporting from patients is accurate.
Words were corrected. I added “passing gas”

Introduction:

Line 40 the reference 1 uses a bracket and parenthesis.
corrected

Line 50, the authors states that the RCT from Currow is biased, preventing us from interpreting it properly. It must be justified by explaining why the authors do this statement.
See further comments

Line 56, the precision that the efficacy is proven only in the "early stages" should be provided.
corrected

Line 58-60, the authors state that octreotide in addition to supportive care resulted in being effective in restoring stool emissions, in my opinion, this statement is very questionable as it cannot be assumed that this is octreotide that was responsible for this. Especially as the available literature does not report the efficacy of octreotide is restoring stool emissions, but only on diminishing the secretions resulting in a mitigation of nausea, vomiting and pain.

I disagree, as in many patients the combination (not only octreotide) of drugs allow to restore the transit and eating (Mercadante S, Ferrera P, Villari P, Marrazzo A. Aggressive Pharmacological Treatment for Reversing Malignant Bowel Obstruction. J Pain Symptom Manage 2004; 28:412–16. These cases confirmed previous observations that are the routine outcome in my unit.

For the first case:
The patient received Dexamethasone two days before stool restoration, why do the authors assume that this was not the reason of the stool restoration? Same for the use of an enema.
As mentioned, it is the combination that works.

For the second case, the patient had hypocalcemia that was corrected. Hypocalcemia can be a reason for bowel obstruction. Why do the authors does not assume that this is the cause of the recovery of stools? Same for the use of dexamethasone and for the rotation to fentanyl.
Of course the comprehensive palliative care treatment may help, but I never heard that correction of hypercalcemia resolves MBO.

In the conclusion, why do the authors states that the use of octreotide is aimed to recover stool emission? The litterature, even the cited one, does not support the use of octreotide in this purpose, but the use for limiting secretions and the associated symptoms.
I report octreotide as principal drug of a combination, not as a single drug (see conclusion). I confirm that in most cases an aggressive treatment may allow to regaining the bowel transit and help start to eat.