American Journal of Emergency Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Haloperidol undermining gastroparesis symptoms (HUGS) in the emergency department☆

Rene Ramirez, MD *, Philip Stalcup, MD, Brandon Croft, BS, Michael A. Darracq, MD, MPH

UCSF-Fresno, Department of Emergency Medicine, Fresno, CA, USA
Community Regional Medical Center, Fresno, CA, USA

ARTICLE INFO

Article history:
Received 18 January 2017
Received in revised form 10 March 2017
Accepted 10 March 2017
Available online xxxx

ABSTRACT

Background: Gastroparesis associated nausea, vomiting & abdominal pain (GP N/V/AP) are common presentations to the emergency department (ED). Treatment is often limited to antiemetic, prokinetic, opioid, & nonopioid agents. Haloperidol (HP) has been shown to have analgesic & antiemetic properties. We sought to evaluate HP in the ED as an alternative treatment of GP N/V/AP.
Methods: Using an electronic medical record, 52 patients who presented to the ED w/GP N/V/AP secondary to diabetes mellitus and were treated w/HP were identified. Patients who received HP were compared to themselves w/the most recent previous encounter in which HP was not administered. ED length of stay (LOS), additional antiemetics/prokinetics administered, hospital LOS, and morphine equivalent doses of analgesia (ME) from each visit were recorded. Descriptive statistics, categorical (Chi Square Test or Z-Test for proportion) and continuous (Wilcoxon Signed Rank Test) comparisons were calculated. Statistical significance was considered for two tail p-values less than 0.05.
Results: A statistically significant reduction in ME (Median 6.75 [IQR 7.93] v 10.75 [IQR12]: $p = 0.001$) and reduced admissions for GP (5/52 v 14/52: $p = 0.02$) when HP was administered was observed. There were no statistically significant differences in ED or hospital LOS, and additional antiemetics administered between encounters in which HP was administered and not administered. No complications were identified in patients who received HP.
Conclusions: The rate of admission and ME was found to be significantly reduced in patients with GP secondary to diabetes mellitus who received HP. HP may represent an appropriate, effective, and safe alternative to traditional analgesia and antiemetic therapy in the ED management of GP associated N/V/AP.

1. Introduction

Manifestations of gastroparesis including abdominal pain, nausea, and vomiting are frequently encountered chief complaints in many US emergency departments (ED). Although gastroparesis has not necessarily been found to be directly associated with increased mortality, it is associated with increased hospitalizations and a decreased quality of life [1]. In the absence of published guidelines for treatment of gastroparesis symptoms in the acute or emergent care setting and due to the severity of presenting symptoms, parenteral analgesia and antiemetics are often administered by treating providers after identifying the absence of urgent or emergent conditions and correcting electrolyte and fluid-balance disturbances. Despite often aggressive ED administration of opioid analgesia and antiemetics, hospital admission for symptom control is common and contributes to significant resource utilization [2].

Opioid analgesia, which may be necessary for symptom control, mechanistically contributes to further inhibition of gastric emptying-the putative disorder in gastroparesis. Repeated administration of opioid analgesia also contributes to the potential for dependency [3]. The development of alternative therapies for the treatment of gastroparesis associated nausea, vomiting, and abdominal pain are desired. There is currently limited published literature however regarding alternative ED treatments for gastroparesis. We sought to evaluate the efficacy of haloperidol (HP) in the treatment of gastroparesis (GP) associated nausea (N), vomiting (V), and abdominal pain (AP).

2. Methods

Haloperidol is a medication commonly used off-label in our department amongst residents and attending physicians to treat acute symptoms of GP N/V/AP. Our emergency department is the third busiest in the state of California, has an annual census of over 110,000 patients per year and sees a diverse group of patients, with approximately 90 different ethnic groups represented. Approximately 50% of our patients are Hispanic, of which about 10% speak only Spanish. Fifty-two (52)

☆ Meetings: An abstract only version of this article was presented at ACEP 2016.

* Corresponding author at: UCSF-Fresno, Department of Emergency Medicine, Fresno, CA, USA.
E-mail address: rramirez@fresno.ucsf.edu (R. Ramirez).

http://dx.doi.org/10.1016/j.ajem.2017.03.015
0735-6757/

patients who had received HP as a 5 mg intramuscular (IM) injection in the treatment of GP N/V/AP in the ED between 2012 and 2015 were retrospectively identified using an electronic medical record (EMR) query after local patient safety review board approval and exemption from patient consent. Search terms included gastroparesis, cyclic vomiting, chronic abdominal pain, nausea, vomiting and abdominal pain. Patients were case-matched with themselves on the most recent previous visit for GP N/V/ AP in which HP was not administered. All visits in which HP was not administered were at least 7 days prior to the visit during the same time frame of 2012–2015 in which HP was administered. ED length of stay (LOS), morphine equivalents (ME), disposition, additional antiemetic or prokinetic medications administered, attending and resident provider name, and hospital LOS (if admitted) were recorded from each visit from the EMR. ME was calculated using an online opioid equivalence calculator (http://www.medcalc.com/narcotics.html) using the opioid medications recorded as administered during ED visit. Descriptive statistics, Chi-Square or Z test for proportion for categorical variables and Wilcoxon Signed Rank Test for continuous variables was performed. Statistical significance was considered for two-tailed p values less than 0.05.

3. Results

The median age of the 52 patients identified and enrolled in this study was 32 (range: 21-57 years) and 32/52 (62%) were female. All patients identified and enrolled had previously been diagnosed with gastroparesis secondary to diabetes mellitus by gastric motility testing. HP administration was associated with a statistically significant reduction in hospital admission (5/52 [10%](95% CI 3–21%) v 14/52 [27%](95% CI 16–41%) p-value 0.02) and analgesia administration (Median 6.75 [IQR 7.93] v 10.75 [IQR12] p-value 0.009). There were no statistically significant differences between HP and no HP with regards to ED LOS (Median 9.2 h [IQR 59.92] v 25.4 h [IQR 24.97] p-value 0.128), hospital LOS (Median 43.68 h [IQR 68.68] v 38.42 h [IQR45.44] p-value 0.117), additional antiemetics or prokinetics administered (see Table 1), or resident/attending provider. No dystonic reactions, akasthesia, excessive sedation or cardiovascular complications (torsades de pointes or dysrhythmias) were observed amongst patients who received HP.

4. Discussion

The present study was designed to assess the efficacy of intramuscular haloperidol in the alleviation of abdominal pain, nausea, and vomiting associated with gastroparesis secondary to diabetes as measured by a reduction in the quantity of opioid analgesia administered and hospital admission. Our study did not look at patients who may have gastroparesis secondary to other disorders such as Parkinson's disease, multiple sclerosis or idiopathic processes.

In this retrospective observational study, administration of haloperidol was associated with a reduction in the quantity of opioid analgesia administered as well as hospital admission. Intramuscular haloperidol was not associated with adverse effects in the present observational study however this was not a primary end point.

There is pharmacological reason to believe that haloperidol would be beneficial in the symptomatic management of nausea, vomiting, and abdominal pain including that resulting from gastroparesis. In addition to antipsychotic effects, haloperidol possesses antiemetic and analgesic properties. Haloperidol is a butyrophenone heterocyclic antipsychotic agent which exerts effects on the gastric and cerebral chemoreceptor trigger zone reducing nausea and vomiting. Haloperidol is a dopamine D_2 antagonist and mediates central effects of dopamine [12]. A Cochrane review originally published in 2008 and revised in 2013, indicated efficacy of antipsychotics in the treatment of pain [4].

Previous studies have suggested that HP exerts a mild agonist effect at opioid receptors. Clay and Brougham [5] as well as Simon [6] described opioid binding effects with haloperidol in the late 1970s. Others have suggested that administration of HP may result in a smaller need for administered opioid analgesia due to synergism between HP and opioids [7,8,9].

More recently, there has been suggestion that HP may exert analgesic or synergistic effects through modulation of the sigma opioid receptor [10]. Clinical studies have described significant analgesic effects with HP. Honkaniemi et al. compared intravenous HP (5 mg in 500 mL normal saline) to placebo (500 mL of normal saline) in the treatment of acute migraine headache. Clinically significant pain relief was obtained in 80% of patients receiving HP while only 15% responded to placebo. Sixteen percent of patients receiving HP experienced sedation or akasthesia sufficient for them not to wish to receive HP again however [3]. No sedation or akasthesia was experienced in the present study with IM HP in the treatment of GP N/V/AP. Hickey et al. similarly described the analgesic benefits of HP in the treatment of cannabis hyperemesis syndrome [11].

Roldan and Chathampally describe a small randomized placebo-controlled trial of a single intravenous dose of HP 5 mg plus "conventional" therapy versus placebo and standard therapy in the treatment of emergency department patients with GP associated N/V/AP. Five patients received HP and 7 patients received placebo. At 1-hour post administration, there was greater reduction in pain score with HP administration versus placebo. However, the authors do not describe what "conventional" therapy entailed nor secondary endpoints such as ED LOS or disposition in the brief abstract [13].

4.1. Limitations

This is a retrospective descriptive analysis limited to the information available in an electronic medical record. Errors may have been made in data entry during emergency department evaluation. There may be additional cases where HP was administered, were lost to follow-up, or were missed in analysis due to a lack of or inappropriate coding. Due to the small sample size of the present case-control series, additional cases have the potential to dramatically change the results. Even with small numbers however, the reduction in opioid administration and hospital admission with HP is robust enough to demonstrate statistical significance. All enrolled patients had at least one week interval between HP administration and previous visit where HP was not administered. This was an intentional attempt to limit the effects of previously administered medications in the ED treatment of GP N/V/AP in determining the effect of HP. This interval is more than 5 half-lives of the common medications administered in the ED and it is unlikely that this significantly affected the results. There was also no attempt to record or control medications taken at home prior to ED visit and this theoretically could have influenced the results. As the patients acted as their own control, we feel that it is unlikely that home administered medications would differ significantly between the ED visit in which HP was administered versus not administered. In the present series, patients and providers were not blinded to the administration of HP and this has the potential to obscure the true effects of HP in the treatment of GP N/V/AP. Because this study was conceived and data was collected years following administration, we feel that it is unlikely to have biased the results due to physician or patient knowledge of administered medication or a bias toward discharge or less analgesic administration when HP was administered versus not. Additionally, there were no significant

Table 1
Antiemetics administered.

Additional anti-emetics/prokinetics	HP administered (N = 52)	HP not administered (N = 52)
Erythromycin	1	1
Prochlorperazine	2	1
Ondansetron	30	28
Metoclopramide	10	15
Benadryl	30	20

Please cite this article as: Ramirez R, et al, Haloperidol undermining gastroparesis symptoms (HUGS) in the emergency department, American Journal of Emergency Medicine (2017), http://dx.doi.org/10.1016/j.ajem.2017.03.015

differences in which resident or attending physicians were involved between visits making provider bias less likely an explanation for the findings of a reduction in analgesic administration or hospital administration. Similarly, there was no difference in the administration of additional prokinetic (erythromycin, metoclopramide) or antiemetics administered between groups making a difference in administered medications between groups less likely an explanation for the observed findings. As the dose of HP administered was 5 mg intramuscular in the present series, it is not known what effect intravenous HP or at differing doses has on clinical efficacy. Our interpreted evaluates patients from a single hospital and may not necessarily be reflective of every ED population. Further studies utilizing multicenter data would offer better insight into general use of haloperidol for the treatment of patients who present to the ED with gastroparesis associated nausea/vomiting and abdominal pain.

5. Conclusion

The rate of hospital admission and amount of opioid administered was found to be statistically significantly reduced in patients with gastroparesis secondary to diabetes who received haloperidol as compared to when not administered. Haloperidol administration at a dose of 5 mg intramuscularly was not associated with adverse effects in the present series. Haloperidol may represent an appropriate, effective, and safe alternative to traditional analgesia and antiemetic therapy in the emergency department management of gastroparesis-associated nausea, vomiting, and abdominal pain.

Grants/financial support

None.

Conflicts of interest

None.

Author contributions statement

N/A.

References

[1] Bielefeldt K. Factors influencing admission and outcomes in gastroparesis. Neurogastroenterol Motil 2013;25(5):389–98:e294.
[2] Hasler WL. Emerging drugs for the treatment of gastroparesis. Expert Opin Emerg Drugs 2014;19(2):261–79.
[3] Honkaniemi J, Liimatainen S, Rainesalo S, Sulavuori S. Haloperidol in the acute treatment of migraine: a randomized, double-blind, placebo-controlled study. Headache 2006 May;46(5):781–7.
[4] Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. Cochrane Database Syst Rev 2013 Aug 29; 8:CD004844. http://dx.doi.org/10.1002/14651858.CD004844.pub3.
[5] Clay GA, Brougham LR. Haloperidol binding to an opioid receptor site. Biochem Pharmacol 1975;24:1363–7.
[6] Simon EJ. The opiate receptors. Neurochem Res 1976 Feb;1(1):3–28.
[7] Maltbie AA, Cavenar Jr JO. Haloperidol and analgesia: case reports. Mil Med 1977 Dec;142(12):946–8.
[8] Maltbie AA, Cavenar Jr JO, Sullivan JL, Hammett EB, Zung WW. Analgesia and haloperidol: a hypothesis. J Clin Psychiatry 1979 Jul;40(7):323–6.
[9] Colclough G, McLarney JT, Sloan PA, McCoun KT, Rose GL, Grider JS, et al. Epidural haloperidol enhances epidural morphine analgesia: three case reports. J Opioid Manag 2008 May–Jun;4(3):163–6.
[10] Cobos EJ, Baeyens JM. Use of very-low-dose methadone and haloperidol for pain control in palliative care patients: are the sigma-1 receptors involved? J Palliat Med 2015 Aug;18(8):660.
[11] Hickey JL, Witsil JC, Mycyk MB. Haloperidol for treatment of cannabinoid hyperemesis syndrome. Am J Emerg Med 2013 Jun;31(6):1003:e5-6.
[12] Büttner M, Walder B, von Elm E, Tramèr MR. Is low-dose haloperidol a useful antiemetic?: a meta-analysis of published and unpublished randomized trials. Anesthesiology 2004 Dec;101(6):1454–63 (PubMed PMID: 15564955).
[13] Roldan C, Chathampally Y. Haloperidol vs placebo in addition to conventional therapy to treat pain secondary to gastroparesis in the emergency department. (Abstract). J Pain 2015 April;16(4) (Supplement, S34).

Please cite this article as: Ramirez R, et al, Haloperidol undermining gastroparesis symptoms (HUGS) in the emergency department, American Journal of Emergency Medicine (2017), http://dx.doi.org/10.1016/j.ajem.2017.03.015