What is the Evidence for the Pharmacological Management of Nausea and Vomiting in Inoperable Malignant Bowel Obstruction?

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Abstract

The objective is to systematically review the evidence available for the pharmacological management of nausea and vomiting in inoperable malignant bowel obstruction. PubMed, EMBASE and clinicaltrials.gov were searched using the following terms: Nausea, Vomiting, Cancer, Inoperable Bowel Obstruction, Malignant Bowel Obstruction. The search identified 699 studies and 1 from an additional source. With the inclusion and exclusion criteria applied 12 papers were selected. Of the 12 studies, 6 RCTs were identified that compared the somatostatin analogue octreotide or lanreotide. Two of these RCTs also compared octreotide to hyoscine butylbromide, and four with placebo. Octreotide was shown to significantly reduce nausea and vomiting. One study however, found that octreotide did not significantly reduce vomiting compared to a placebo. Prospective studies, retrospective studies and non-randomised clinical trials were also identified. They assessed the use of octreotide, granisetron or olanzapine. They found that there was significant improvement in nausea or vomiting episodes. Despite not being the first line treatment Octreotide appears to be the most studied and researched drug. In all but one study it has been found to have a positive outcome. This review has highlighted the lack of information or research available on other antiemetic or anti-nausea medications, despite their widespread use.

Introduction

The management of bowel obstruction is a common clinical challenge in patients with advanced cancer (Mariani et al. 2012). Inoperable malignant bowel obstruction (IMBO) is a major cause of nausea and vomiting arising on a background of damage to the intestinal epithelium (Mariani et al. 2012). This imposes a complex clinical situation that requires multidisciplinary efforts, including palliative physicians, surgeons and oncologists (Lee et al. 2018). The principal management of IMBO is conservative due to the increased risk of morbidity and mortality associated with surgery (Cousins et al. 2016). Moreover, the value of surgery in alleviating symptoms is questionable (Mariani et al. 2012). Treatment is likely to incorporate intravenous hydration alongside pharmacological treatment and in severe cases, parenteral nutrition (Ripamonti et al. 2001).

Pharmacological treatment includes anti-emetics, antisecretory agents, analgesics and corticosteroids (Cherny 2004). Multiple studies have supported the use of dexamethasone, prednisolone, hyoscine butylbromide, somatostatin analogues, and chlorpromazine in alleviating nausea and vomiting like symptoms (Hardy et al. 1998; Laval et al. 2000; Ripamonti et al. 2001; Mercadante et al. 2000; Mittal et al. 2014; Obita et al. 2016). Metoclopramide along with intravenous PPI's (Proton Pump Inhibitors) such as omeprazole and corticosteroids are also used to alleviate symptoms of nausea and vomiting in IMBO (Tookman 2000; Laval et al. 2000). A nasogastric tube (NGT) might be required to drain stomach contents if drug control does not alleviate symptoms, however this can be particularly distressing for patients. Thus, effective drug therapy in terminally ill patients is needed (Hisanaga et al. 2010). The somatostatin analogue, octreotide, has more rapid effects than hyoscine butylbromide in reducing gastrointestinal secretions (Peng et al. 2015). Octreotide is one of the primary

agents used in IMBO with lanreotide as an alternate. Like the hormone somatostatin, these agents have similar physiological effects including splanchnic blood vessel vasoconstriction, decreased secretions by the intestine and pancreas, lower water and electrolyte absorption in the GI Tract, and changes in gut motility (Gilbar 2000; Obita et al. 2016). Octreotide has emerged as a widely used agent in combination with other anti-emetics and analgesics (M. et al. 2013). However, despite its efficacy, the cost of this agent is higher than other anti-secretory drugs used in IMBO (Mercadante et al. 2000).

Nausea and vomiting are distressing symptoms in patients with advanced cancer (Glare et al. 2011). It requires careful clinical assessment of the patient's symptoms and knowledge of the available therapeutics for palliating them (Glare et al. 2011). To help clinicians utilize the most effective treatments for symptom control, we will examine the pharmacological options investigated in original scientific literature, with the goal of providing optimal palliative care and QOL of patients with IMBO.

Methods

PubMed, EMBASE and clinicaltrials.gov were searched for articles published between 1990 and 2018 (Figure 1). Eligible studies met the following criteria: patients with cancer, over 18, receiving pharmacological intervention for nausea and vomiting related to inoperable malignant bowel obstruction. In order to select for the population of interest, all types of studies were considered, including Randomised Control Trials (RCTs), prospective studies and retrospective studies. Phase II/III clinical trials were also considered. Searches were limited to studies published in the English language and only original research was included. The outcome measured was the improvement of nausea or vomiting after administration of pharmacological intervention.

Studies were excluded if the nausea and vomiting was related to opiate use, chemotherapy or radiotherapy. The following search terms were used: Nausea, Vomiting, Cancer, Inoperable Bowel Obstruction, Malignant Bowel Obstruction (Figure 1). A Boolean

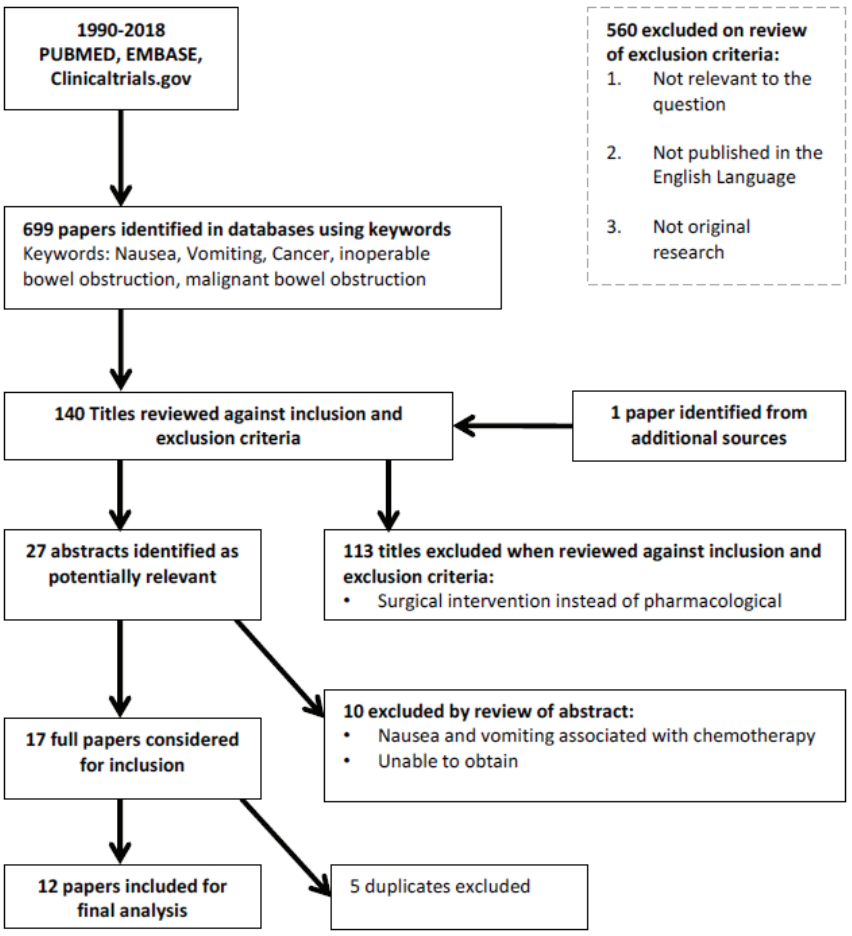

Figure 1. Flow chart of data selection

search strategy, as follows was used: "Nausea" OR "Vomiting", AND 'inoperable bowel obstruction' OR 'malignant bowel obstruction' AND "Cancer".

Data Extraction

Refer to Table 1.

Results

Studies

We identified 699 unique studies through the searches and 1 paper identified by a clinical medicine lecturer within palliative care. Twelve studies were included in the final analysis. Six of these studies were RCTs (Randomised Controlled Trials) investigating pharmacological treatment for IMBO met our inclusion criteria (Figure 1).

Study characteristics

Six RCTs were identified comparing the somatostatin analogue octreotide or lanreotide. Two of the RCTs also compared octreotide to hyoscine butylbromide, and four with placebo. Four of the trials were single centre studies, and two trials were multicentre. The majority of the trials identified were conducted in Europe, with one being performed in China and America. As the studies examined different interventional outcomes and primary/secondary endpoints, it was not possible to perform a meta-analysis.Both studies found that octreotide significantly reduced episodes of vomiting compared with hyoscine butylbromide in patients with advanced cancer. Studies comparing octreotide to placebo found it be more effective in symptom management, however this was only conclusive in two of the three identified due to premature termination of one study. The study by Currow et al 2014, in contrast found that octreotide did not significantly reduce vomiting compared to a placebo.

In addition to the RCTs, 2 prospective studies, 1 retrospective study and 3 non- randomised clinical trials were also identified. Five of these studies assessed the use of octreotide, one assessed the use of Granisetron

Author/Year	N =	Study Design	Primary Outcome	Drug used	Primary Diagnosis	Setting	How Nausea or Vomiting Outcomes Were Measured	Summary and Main Findings
(Hisanaga et al. 2010)	43	Multicentre prospective study	Overall improvement of subjective abdominal symptoms.	Octreotide	Gastric, Pancreatic, Colorectal, Ovarian, Endometrial, Bile duct, Cervical, Gall bladder, and others	Octreotide 300μg/day IV/SC for 3 days. Following an assessment, the dose was adjusted up to 600μg daily if required.	Self-rating scores selected from the MD Anderson Symptoms Inventory and Kurihara's Face Scale. Any change in symptoms was then evaluated on day 8.	Nausea, vomiting and abdominal pain was reduced in 59–72% of the patients.
(Shima et al. 2008)	25	Clinical trial	A change in vomiting episodes after treatment	Octreotide	Gastric, Colon, Ovarian, Pancreatic, Cervical cancers	Octreotide 300μg/day SC for 6 days. Patients who responded to 6-day course continued to receive drug. Dose decreased to 150μg/ day if marked nausea/vomiting.	Number of vomiting episodes and severity per day. Severity was graded using the Toxicity criteria of the Japan Clinical Oncology Group.	44% responded to treatment with resolution or improvement of nausea/vomiting
(Mystakidou et al. 2002)	68	RCT	Improvement of nausea, vomiting and abdominal pain in patients with MBO	Octreotide	GI, Abdomen, and Pelvic cancers	SC Hyoscine Butylbromide 60-80mg/day VS SC Octreotide 600-800 microgram/day.	Patient diary cards	Nausea and vomiting was reduced in the patients receiving Octreotide
(Kubota et al. 2013)	14	Clinical trial	Improvement of oral intake, subjective symptoms, and NGT	Octreotide	Urological cancer	Octreotide 300μg/day SC as a continuous injection.	Grading of Vomiting by World Health Organisation Toxicity Criteria	Overall response rate was 92.8%. 28.6% had "no vomiting". 64.3% had a "reduced vomiting".
(Peng et al. 2015)	97	RCT	Determine whether octreotide or scopolamine butylbromide was more effective at controlling GI symptoms in MBO.	Octreotide and Scopolamine butyl-bromide	Ovarian cancers	Octreotide 0.3mg/day (n=48) or scopolamine butylbromide 60mg/day (n=49) for 3 days through a continuous SC infusion.	Vomiting, nausea, dry mouth, drowsiness, GI secretions via NG tube, and continuous or colicky pain were measured using Likert scales.	Symptoms of nausea and vomiting, and GI secretions, were reduced in the group administered Octreotide in comparison to group given Scopolamine butyl-bromide
(Mercadante et al. 2000)	18	RCT	Octreotide vs. Hyoscine butylbromide as effective anti-secretory drugs for in states of inoperable MBO.	Octreotide and Hyoscine butyl-bromide	Small bowel, vulva, ovarian, pancreas, rectal, breast, liver, stomach cancers.	Octreotide 0.3mg/day (n=9) or hyoscine butyl-bromide (HB) 60mg/day (n=9) SC.	Episodes of vomiting, nausea, drowsiness, continuous and colicky pain were measured using a Likert scale	Octreotide induced a significant reduction in the number episodes of vomiting and intensity of nausea compared with HB treatment
(Tuca et al. 2009)	23	Multicentre Open-label Phase II Clinical Trial	Improvement of symptoms of nausea and vomiting due to inoperable MBO.	Granisetron	GI, Genealogical, and other cancers	Granisetron 3mg/day IV and dexamethasone (4mg IV BD). Optional haloperidol (2.5mg SC) was retained for rescue therapy.	Numeric scale evaluated nausea, pain, asthenia, anorexia at baseline and every 24 hours until four days of treatment.	A significant decrease in the severity of nausea and number of episodes of vomiting. Nausea and vomiting control achieved in 86.9%
(Khoo et al. 1994)	24	Phase I/II Study	Symptom improvement in patients with intractable vomiting, inoperable MBO	Octreotide		SC infusion of octreotide (median initial dose 300, range 100–600μg/day).	Number of vomiting episodes and volume of NG aspirate were measured	Vomiting controlled or the volume of nasogastric aspirate was reduced in 75% of patients.
(Kaneishi et al. 2012)	20	Retrospective study	Assess antiemetic activity of olanzapine in cancer patients with incomplete bowel obstruction.	Olanzapine		2.5-7.5mg/day over a range of 2-60 days.	Two doctors interpreted the electronic charts of 20 patients. The severity of symptoms was evaluated on a scale of 0 to 3	90% had decreased intensity of nausea and frequency of vomiting decrease from an average of 1.1 times/day to 0.3 times/day
(Mariani et al. 2012)	80	Randomized, DB, Placebo Controlled Phase III Study	Reduction in number of vomiting episodes and/or NG volume aspirate.	Lanreotide	Peritoneal carcinomatosis	30mg injection of lanreotide microparticles (n=43) or placebo (n=37) every 10-days until they requested to stop or died	Visual analogue scales for nausea. Episodes of vomiting per day, volume of NG aspirate.	Symptom control was better in the group receiving lanreotide.
(Novartis, 2011)	64	Randomised Interventional DB, Controlled Trial	Treatment of symptomatic inoperable bowel obstruction in peritoneal carcinomatosis	Octreotide	Peritoneal carcinomatosis	Octreotide long-acting release 30mg IM/28days for 90days, and immediate-release Octreotide 600μg/day SC BD/TDS or IV 24-hrs	Number of vomiting episodes per day and volume of NG aspirate was measured.	Study was terminated prematurely due to low enrolment
(Currow et al. 2015)	87	Randomised Control Double blind study	Patient-reported days free of vomiting at 72 hrs	Octreotide		SC infusion of octreotide (600 mg/24 hours) co	Number of days free of vomiting	17 octreotide patients had 72 hrs free of vomiting, compared to 14 placebo patients. No significant difference comparing treatments.

Table 1. Table of articles and data extraction from the papers selected for full analysis.

and one also assessed the use of Olanzapine (Table 1). Each of these studies found that there was significant improvement in nausea or vomiting episodes.

Demographics

The number of patients per study averaged at 47 (range: 14-97). All studies focused on the treatment of nausea and vomiting related to IMBO. Nausea related to chemotherapy and pain management was excluded from consideration. Primary diagnosis ranged hugely in the total patient cohort, but abdominal and pelvic cancers were the most frequently occurring. The route of administration was predominantly subcutaneous infusion (Hisanaga et al. 2010; Shima et al. 2008; Mystakidou et al. 2002; Kubota et al. 2013; Peng et al. 2015; Mercadante et al. 2000; Khoo et al. 1994; Novartis Pharmaceuticals 2011). Due to the nature of the symptoms being examined, oral medication was not an option apart from in the case of olanzapine (Kaneishi et al. 2012). In some cases, intramuscular injection (Mariani et al. 2012; Novartis Pharmaceuticals 2011) and intravenous administration (Novartis Pharmaceuticals 2011; Tuca et al. 2009; Hisanaga et al. 2010) were used.

Assessment of symptom severity and improvement also varied between papers. Four studies used a Likert scale, with scores ranging from 0-3 based on severity. Two used diary cards and two others used the WHO vomiting toxicity criteria. Patient questionnaires, nasogastric aspirate volume and the MDASI (MD Anderson Symptoms Inventory score) and Face Scale Score were used one time each.

Discussion

IMBO is a complex clinical challenge in many advanced cancers. The management of this issue appears to involve multidisciplinary efforts and there is little guidance in treatment based on the current literature. This review analysed the pharmacological management of preventing vomiting and nausea in IMBO. Twelve papers were identified that fit our inclusion criteria, from an original 140 reviewed against inclusion and exclusion criteria.

The Oxford Handbook of palliative care outlines the current choices of antiemetic drugs in IMBO. It recommends cyclizine, Hyoscine butylbromide, octreotide or ondansetron, which can all be given subcutaneously to manage the symptom of vomiting (Tookman 2000). This should follow the use of metoclopramide, cyclizine or haloperidol as first line followed by a combination with ondansetron or cyclizine to alleviated emesis (Tookman 2000). Broad-spectrum antiemetics such as levomepromazine can also be employed (Tookman 2000). On reviewing the current treatment guidelines, it is surprising that other antiemetic agents were not identified by the search. Despite not specifying a particular pharmacological intervention in the search, 9 out of the 12 papers focussed on octreotide. This highlights the need for further research regarding these medications to confirm their clinical efficacy, as little information is currently freely available (Tookman 2000).

As discussed previously, octreotide was the primary agent investigated to manage symptoms in IMBO in the majority of studies. Lanreotide, hyoscine butylbromide, olanzapine and granisetron were also shown to have clinical benefit however more research is needed to confirm their efficacy in clinical practice. As the average number of participants in each of the trials was only 47, further research with larger cohort studies, ranging from multi-centre to international studies is needed to ensure primary endpoints can be assessed (Table 1).

The study by Currow et al 2015 was the only study identified which highlighted that Octreotide, when compared to a placebo, did not significantly reduce nausea and vomiting (Currow, 2015). As a randomised control trial, it was well designed and the results do carry significance, however it is not sufficient to invalidate the other trials, which all found positive outcomes. The trial did find that vomiting episodes were reduced, however it was not statistically significant. The trial assessed improvement after 72 hours and this may not be a sufficient time frame for clinically significant results to occur. The outcome may have been different if the patients had been followed for a longer period of time. In general, most studies have shown that octreotide has a positive response for the treatment of nausea and vomiting. It has also very few side effects and so can be safely given. Furthermore, the side effects that do occur cannot always be linked directly to octreotide due to the nature of patients being on multiple medications and having complicated illnesses.

In a number of studies, there was continued co-administration with other antiemetics such as prochlorperazine or haloperidol. In one study their use was continued and only had to be documented until

day 4, until the first assessment had been completed. Following this there was then no restriction on their use and symptoms were reassessed at day 8 (Hisanaga et al. 2010). This co-administration has the potential to bias the results. It also highlights the difficulty of studies within palliative care, as ideally the effect would be determined in isolation, however this is not always possible or ethical in patients with terminal illness.

In addition, a limitation in the cohort of patients examined is the type of scale used to determine symptom severity. Some of the studies utilised a likert scale. The Likert scale is used to represent a person's attitude to a topic, in this case vomiting and nausea. It ranges from 0-3 with 0 represent no response, 1 slight response, 2 moderate response and 3 severe response (Peng et al. 2015; Mercadante et al. 2000). There is potential for bias using this scale as what one patient deems a slight response, another may think is severe. However, the goal of treatment is to improve how a patient feels about their illness and not what patient has more severe symptoms. In the multicentre prospective study on efficacy and safety of octreotide for inoperable malignant bowel obstruction, the Face Scale Score was used in conjunction with an MDASI score, which is an 11-grade numerical scale. In this study, the MDSAI score showed significant improvement with octreotide treatment, however the improvement was less significant when using the Face Scale score. This may be due to the subjective nature of the Face Scale Score and that quality of life and therefore happiness may be reduced due to disease progression and not because of nausea and vomiting. This also highlights the disparity between assessment methods, and further research is needed to find a suitable, less subjective assessment method, which would allow easier comparison between studies (Hisanaga et al. 2010).

Grading of vomiting by the WHO toxicity criteria and the method of counting the number of vomiting episodes were other methods used, we found these methods were less subjective and so gave a more accurate description of a drug's efficacy. However, the method of counting the number vomiting episodes did not always quantify the volume of vomit produced and therefore comparison is made more challenging (Kubota et al. 2013; Peng et al. 2015; Khoo et al. 1994; Mariani et al. 2012).

In undertaking this review it has highlighted that the area of palliative medicine in general is difficult to research due to ethical obstacles and patients' medical conditions. A study by Chan et al, 2014 highlighted the barriers that are difficult to overcome in regards to research within palliative care. Within this study they systematically identified barriers by interviewing 61 lead researchers within the palliative care field. One of the key challenges identified was the study population and topic. Within the interview one researcher stated "The work we do by its nature is challenging and always will be. It's hard work to do research with such a vulnerable patient population and their families. It's hard to recruit them, it's hard to follow them." The study also identified the other unique challenges that face researchers within this setting and how often doctors are very reluctant to change their standard practices of care within a very distressed, vulnerable and dying population (Chen et al. 2014).

We found a high attrition rate in many of the studies and trials due to decline in patient's well-being and death during the study. This is demonstrated by the multi-centre prospective study determining the efficacy and safety of octreotide for inoperable malignant bowel obstruction (Hisanaga et al. 2010). This study had an attrition rate of 13% (n=6). Initially 49 patients were enrolled, however 3 ineligible patients were excluded due to delirium or lymphoma. A further 3 patients were discontinued due to reduced consciousness, protocol violation or not all data was available (Hisanaga et al. 2010). This is also apparent in those trials terminating prematurely due to high patient withdrawal (Novartis Pharmaceuticals 2011).

Conclusion

In conclusion, octreotide appears to be the most studied and researched drug, despite not being the first line treatment. In all but one study it has been found to have a positive effect on nausea and vomiting in patients with malignant bowel obstruction. It must be noted however that there is a lack of information or research available on other antiemetic or anti-nausea medications. Furthermore, a key limitation is also the small numbers participating in the trials, however due to the nature of the illness it may still prove challenging to recruit participants on a larger scale. It may also be advantageous for a more reliable and less subjective scale or assessment method to be produced. This would allow more comparison between studies and remove bias, leading to more meaningful results.

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