

Management of nausea and vomiting in advanced disease



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In patients with advanced disease, nausea and vomiting are common and distressing symptoms. Established antiemetics frequently result in good symptom control. However, a number of patients present with intractable symptoms. A newer class of antiemetics, the neurokinin-1 antagonists, addressing a different type of receptors in the emetogenic pathway, have shown additional antiemetic benefit in chemotherapy and postoperatively.

Objective

To evaluate the effectiveness of NK1-receptor antagonists in the management of nausea and vomiting in advanced disease.

Data sources and search strategy

The electronic databases Embase, Medline and PsycINFO were searched using the basic search strategy (“ neurokinin-1 antagonist”) AND (“ nausea” OR “ vomiting”), modified for each database.

Selection criteria

Meta-analyses, systematic reviews, randomised controlled trials (RCTs), cohort/case-control studies, case series and single case reports of NK1-receptor antagonists for the treatment of nausea or vomiting or both, in any advanced disease setting.

Results

The search strategy identified 1702 titles of which one study was obtained in full and then excluded. The hand search revealed five titles as potentially meeting the inclusion criteria: One RCT protocol that was withdrawn before enrolment, one study that could not be obtained, 3 more cases that had to

be excluded based on study type. Therefore, no studies could be included in this review.

Conclusion

There is insufficient evidence for the use of NK1-antagonists for the management of nausea and vomiting in advanced disease. To guide our clinical decision in this patient population, we need better evidence of effectiveness of NK1-antagonists.

Introduction

Symptom Prevalence

In patients with advanced disease, nausea and vomiting are common and distressing symptoms. The prevalence of nausea and vomiting in cancer and non-cancer palliative care patients has been reported to be between 6-68%, nausea generally having a higher prevalence. 1-7

Nausea is most prevalent in gynaecological and gastrointestinal cancer, 4 and has shown to be an independent prognostic factor for survival in advanced cancer patients; 3 Jiménez et al. identified nausea and vomiting together as a gastro intestinal symptom cluster in 23% of their patients with advanced cancer. 8

Pathophysiology of nausea and vomiting

Definition

Vomiting (or emesis) is the expulsion of gastric contents through the mouth, caused by a forceful and sustained contraction of the abdominal muscles and diaphragm. 9

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Nausea is an unpleasant feeling of the need to vomit that often accompanies emesis and is associated with autonomic symptoms like pallor, cold sweats, tachycardia, and diarrhoea. 10

Why do we experience nausea and vomiting?

From an evolutionary perspective, vomiting acts as important mechanism of protection against food poisoning. Furthermore, nausea seems to lead to food aversion in order to avoid future ingestion. 11, 12 The vomiting reflex is present in many species, but not in all. Several common laboratory animals (e. g., rat, mouse, guinea pig and rabbit) lack this emetic response. 11, 13

Mechanisms

Nausea and vomiting are two distinct but related entities. 13, 14 A variety of stimuli can trigger nausea and vomiting, including many forms of medical treatment. 15, 16 In advanced cancer or progressive disease we typically see multifactorial causes of nausea and vomiting. 10, 17, 18

What is known about the neurophysiology of the vomiting reflex mainly comes from animal models of the ferret, the dog and the cat 13, 19, 20 although there have been studies in humans. 21, 22

Less evidence exists with regard to nausea, as it is difficult to establish animal models due to the subjective nature of the symptom. 13 However, nausea has been associated with increased levels of anti-diuretic hormone and oxytocin as well as gastric dysrhythmia. 11, 13 The neural system seems to be at least partly distinct from the emetic pathways 13 there is for

example an increased activity of the inferior frontal gyrus associated of the human cerebral cortex with nausea. 21

Physiology of the emetogenic pathways

Vomiting center

Vomiting is a complex somato-visceral process, presumably coordinated by the vomiting centre or 'vomiting pattern generator'. 23 The vomiting centre coordinates input from at least 4 pathways, then resulting in a the somatic and autonomous efferent output of the vomiting reflex 10, 14, 24-27 (Figure 1).

The vomiting centre (diffusely distributed neurons, rather than a well localised area)¹⁹ is located in the third ventricle, fully within the blood brain barrier and adjacent to centres that are responsible for respiration and salivation. 10 The nucleus of the tractus solitarius (NTS) forms part of the vomiting centre. 27

Figure 1. Pathways and neurotransmitters involved in nausea and vomiting:
Adapted from multiple sources 14, 24-27

CTZ = chemoreceptor trigger zone; NTS = nucleus of the tractus solitarius; CTX= chemo therapy, RTX = radiotherapy; Receptors: Achm = muscarinic cholinergic; H1 = histamine type 1; GABA= GABA = gamma amino butyric acid; D2 = dopamine type 2; 5HT_{2, 3, 4} = serotonin receptor subtypes 2, 3 and 4; $\hat{1}\frac{1}{4}$ = $\hat{1}\frac{1}{4}$ opioid; NK1 = neurokinin-1; ... incompletely understood;

The chemoreceptor trigger zone (CTZ)

Emesis is often chemically induced. 27 The main CTZ is located outside the blood brain barrier in the area postrema at the bottom of the 4th ventricle and is sensitive to emetic agents such as high calcium levels, urea, morphine, and a variety of cytotoxic agents in the blood and cerebro-spinal fluid. 10, 27

The cerebro-cortical pathway

Cerebro-cortical influences of vomiting and nausea include input from the five senses, fear, anxiety, learned behaviour after experiencing chemotherapy, but also direct effects such as meningeal irritation and raised intracranial pressure. 26 Descending fibres from the higher centres may stimulate or inhibit the vomiting centre. 14

The vestibular pathway

Triggers for nausea and vomiting are inputs from motion and labyrinth disorders or vestibular damage by tumours or drugs. 26, 27 The projections from the vestibular system are incompletely understood. 14

Peripheral pathway

The main input from the periphery is caused by mechanoreceptors (which detect distension or direct invasion in the GI tract) and chemoreceptors (which detect acids, irritants and probably bacterial toxins) in the gastrointestinal tract and liver. 18, 28 There are also afferent impulses from the heart, pharyngeal stimulation and taste through the vagal nerve, splanchnic nerves, glossopharyngeal nerves and the chorda tympani of the

facial nerve. The impulses are mainly travelling to the nucleus of the tractus solitarius. 26, 27

Principles of therapy

The current paradigm in palliative care is to base the antiemetic treatment on a careful history, focused clinical examination and appropriate investigations. 14, 29, 30

This approach not only helps excluding reversible causes (e. g., hypercalcemia, hyponatremia and infection) 31, but also enables identifying the presumed underlying aetiology (e. g., gastric stasis, biochemical causes, raised intracranial pressure, and ileus. 9, 15, 30

This presumed aetiology can then guide the choice of antiemetic based on both, the neuropharmacology of the emetogenic pathway, 14, 27, 29 and the current understanding of the affinity of drugs to different receptors 14, 32 (Table 1). This generally is supplemented by non-pharmacological treatments. 18, 29

If first line treatment fails, there is a rationale to add other drugs acting on complementary receptors 26, 33 or antiemetics with a broad spectrum of pathways covered. 34, 35

However, there is also a second equally effective, empiric approach to treatment 24, 33 that might be preferred, especially near death, where investigations identifying underlying aetiology might not be warranted any longer. 36

Table 1. Receptor affinity of antiemetics

Putative site of action

CTZ

Vestib.

Cortex

VC

Vestib.

VC

VC

GIT

CTZ

GIT

Cortex

CTZ

VC

GIT

Receptors

D2

H1

Achm

5HT2

5HT3

NK1

5HT4

central

central + peripheral

peripheral

Metoclopramide

++

+

++

Domperidone

++

Scopolamin

+++

Cyclizine

+++

++

Dimenhydrinat

++

+

Ondansetron

+++

Haloperidol

+++

Levomepromazine

++

++

++

+++

Olanzapinea

+

+

+

++

Aprepitanta

+++

Adapted from Bausewein and Werni-Kurik^{37, 38}; a adapted from Glare⁹;

CTZ = chemoreceptor trigger zone; VC = vomiting centre; GIT =

gastrointestinal tract; Vestib. = vestibular apparatus

Effectiveness of current treatment

Using different classes of established antiemetics results in good symptom control in up to 93% of palliative care patients. ^{15, 17, 30} However, that leaves a number of patients that present with intractable symptoms ^{26, 30} and the management of these patients can be challenging. ²⁷ For those patients it would be desirable to have additional means of treatment available. ³⁵

Neurokinin-1 (NK1) antagonists

A newer class of antiemetics, the neurokinin-1 (NK1) antagonists ³⁹ have shown significant additional antiemetic benefit in highly emetogenic chemotherapy ^{40, 41} as well as postoperatively ⁴² and are included in current international guidelines. ⁴³ From a pathophysiological perspective NK1 antagonists address a different type of receptors in the emetogenic pathway. ⁹ These receptors are widely distributed and therefore NK1-antagonists have been referred to as broad spectrum antiemetics. ^{14, 39} Some authors in the last years suggested that good quality studies on NK1-antagonists should be performed to evaluate the effectiveness in a palliative care population. ^{14, 17, 29}

Current evidence

Outside of chemotherapy-induced and post-operative nausea and vomiting, previous systematic reviews on the effectiveness of antiemetic treatment by Glare (2004) 17 and Davis, (2010) 33 could not show any evidence for the use of NK1 antagonists. Both reviews focused on cancer patients only and were limited to the English language. In addition, they paid no specific attention to NK1receptor antagonists in their search strategy and only included studies until 2008. 33

Objective

More than two years later, the purpose of this review is to assess the effectiveness of NK1 receptor antagonists in controlling nausea and vomiting in patients with advanced disease.

Methodology

This systematic review followed current standards from the Centre for Reviews and Dissemination. 44 The assessment of studies was based on level of evidence and reported outcome.

Definition of advanced disease:

Advanced disease: 1, 45 Active and progressive illness with a limited prognosis (the prognostication relates to different factors such as symptoms, performance status and disease trajectory and therefore is disease specific), or being in hospice or palliative care.

Search strategy:

The search strategy was adapted from Glare. 17

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Bibliographic databases:

EMBASE 1980 to 2011 Week 15

Ovid MEDLINE (R) 1948 to April Week 1 2011

PsycINFO 1806 to April Week 2 2011

Basic search terms for electronic databases:

Neurokinin-1 (NK1) receptor antagonist AND

Nausea OR vomiting

The search terms were adapted for each database, where possible using appropriate exploded Medical Subject Headings (MeSH) terms. The search was updated on 17 April 2011. For the detailed search strategy, see appendix 1.

Other sources:

To identify any articles missed by the electronic database I search the following additional sources were searched or contacted:

The drug information of Emend™ (aprepitant)⁴⁶ and as a result

The local branch of the manufacturer of Emend™, Merck-Sharp&Dohme in Austria and a pharmacist (C. R.) with a palliative care background were contacted.

The International Clinical Trials Registry Platform to identify unpublished studies using the individual NK1-antagonists as search terms (aprepitant,

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fosaprepitant, casopitant, netupitant, rolapitant, vestipitant, ezlopitant, orvepitant, lanepitant and dapitant).

The bibliographies of articles retrieved and cited for this review, and the Oxford Textbook of Palliative Medicine (4th edition)¹⁴ were hand searched.

The bulletin board of ©Palliativedrugs. com was searched using the search term aprepitant. 47

Due to time constraints, searching additional databases, hand searching the tables of content of major palliative and oncology journals as well as contacting more experts in the field was not possible.

Screening search results:

If the title of the study appeared relevant, the abstract was screened for the following inclusion and exclusion criteria:

1. The study involved humans
2. The study participants had advanced disease
3. The study contained a pharmacological intervention of NK1-receptor antagonists aimed at controlling nausea and or vomiting
4. The study objective was not primarily aimed at evaluating the control of nausea and vomiting caused by emetogenic chemotherapy (CINV), or radiation therapy (RINV), or the control of postoperative nausea and vomiting (PONV)

The full article was retrieved for detailed evaluation only if it was published in English or German and met all of these criteria or, if the abstract seemed potentially relevant, but was inconclusive with regard to inclusion or exclusion criteria.

Types of studies for inclusion in review:

Metaanalyses

Systematic reviews

Randomised controlled trials (RCTs)

Well-designed cohort/case-control studies and

Case series and single case reports

Clinical examples and expert opinions were excluded

Data extraction:

Data was extracted into a table with the following headings: reference, study design, level of evidence, number of patients, setting /population, intervention, duration, reported outcome, reason for exclusion.

Level of evidence:

The level of evidence was graded as followed (adapted from Davis et al.) 33:

Table 2. Levels of evidence

A:

Evidence from RCT (randomised controlled trials)

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B1:

Evidence from single-drug prospective studies or in which single-drug activity could be determined

B2:

Evidence from prospective etiologic guideline trials or multiple drug combination studies in which single-drug activity could not be determined

C:

Evidence from cohort studies, retrospective studies, case series, or single-case reports

—

Not graded as evidence: clinical examples, expert opinions

The quality of RCTs (randomization, blinding, withdrawals and dropouts) would have been determined by the criteria published by Jadad et al.. 48

Quantitative Analysis:

Given the results of previous systematic reviews on nausea and vomiting in cancer patients 17, 33 it was very unlikely to get sufficient data for quantitative analysis. But even with sufficient data it would have been beyond the scope of this limited review due to time constraints.

Results

Electronic databases:

The initial search strategy for the electronic databases Embase, Medline and PsycINFO produced a list of 1702 citations of which only two abstracts appeared relevant. Both papers were identical so one was excluded as duplicate prior to obtaining it in full. 49 It was a case study of severe intractable vomiting due to refractory diabetic gastroparesis in a young woman with poorly controlled diabetes. The study was excluded based on the disease trajectory, which did not meet the definition of advanced disease.

Figure 2. PRISMA chart

Other sources:

Other sources revealed five titles as potentially meeting the inclusion criteria.

One study was a reference in the side effect section of the Austrian drug information sheet of Emend(TM) (aprepitant), referred to as a non-CINV (chemotherapy induced nausea and vomiting)/non-PONV (postoperative Nausea and Vomiting) study where apparently one case of a serious side effect was reported. 46 Contacting the manufacturer and contacting a pharmacist with a palliative care background could not produce the study within the given timeframe and the study was excluded as unobtainable.

In the International Clinical Trials Registry Platform one study protocol of a randomised clinical trial by the Vanderbilt-Ingram-Cancer-Center was identified. 50 It was a protocol for a pilot study to compare the effectiveness

of aprepitant versus ondansetron in treating nausea and vomiting caused by opioids. This study was withdrawn prior to enrolment without giving a reason and therefore was excluded.

Searching the bibliographies of the retrieved and cited articles and the Oxford Textbook of Palliative Medicine (4th edition)¹⁴ resulted in no further studies.

The bulletin board of ©Palliativedrugs. com⁴⁷ however, revealed three messages containing accounts of patient with advanced disease, successfully receiving aprepitant for nausea. With very limited information available on the individual cases, these messages have been considered clinical examples and therefore had to be excluded based on study type.

Therefore no studies could be included in this review (for details of the excluded studies see appendix 3).

Discussion

Summary of evidence

Despite the longstanding call of some authors for good quality research in the advanced disease population, ^{14, 17, 29} this review still failed to identify studies testing the effectiveness of NK1 receptor antagonists in the management of nausea and vomiting in advanced disease.

Only anecdotal accounts from individual palliative care physicians sharing their experience in an internet forum could be found. ⁴⁷ Although good results were reported, the main rationale for the off label use of aprepitant

for patients with intractable nausea is inferring its potential effectiveness and safety from high level evidence in chemotherapy or postoperatively. 41 Those studies only showed short term safety. However, as NK1 antagonists initially were studied for their anti-depressive properties, data of good tolerance of treatment exists for up to 8 weeks duration. 51 It is interesting, that all three reported cases are about successful treatment of nausea only, which is often more difficult to treat in chemotherapy. 40 A potential difference could be the greater role of anticipated nausea in patients receiving chemotherapy. 52, 53, 54 One aspect that needs special consideration in NK-1 antagonists is their influence on cytochrome P450, causing potential interaction with a number of other drugs. 39, 55, 56

The single case report of a 31 years old woman with diabetic gastroparesis showed that the treatment in this individual case was both effective and well tolerated for 4 months, but it was no case of advanced disease. 49

A study protocol of an open label randomised controlled trial by the Vanderbilt-Ingram Cancer Center for a pilot study (comparing the effectiveness of aprepitant versus ondansetron in treating nausea and vomiting caused by opioids in patients with cancer) had the potential for being a good quality study, but was withdrawn prior to enrolment without giving a reason. 50 The significance of this is unclear. With more time at hand, it would have been possible to contact the Center for more information.

With this striking lack of evidence after more than ten years of considerable research on neurokinin receptor antagonists 57 one has to question, whether

it is even feasible to attempt treatment with NK1-antagonists in patients with advanced disease.

Based on our current knowledge of the patho-physiology, in three out of the four presumed emetogenic pathways and in the vomiting centre as the common final pathway, we do find NK1 receptors 12, 25 (Figure 1). This in fact supports the assumption of a potential antiemetic effect.

What else could explain the lack of evidence? It is acknowledged, that it is more difficult to perform clinical studies in the palliative care population due to ethical and practical difficulties. 58 From an industry point of view, the market is probably too small to be of interest. On the other hand for many facilities the high costs compared to standard treatment could be prohibitive, 25, 59 especially in the community setting. Considering the costs caused by untreated nausea and vomiting however, it not only would make a huge difference for the individual patient but potentially could be cost effective as well. 60

Limitations

The main limitation of this review is that, due to time constraints, additional electronic databases, extensive hand search and contact of experts were excluded. In Palliative Care a number of publications might not be included in the searched electronic databases and therefore studies might have been missed. 61 The problem of publication bias for non - RCT's also has to be considered. Another limitation was the single author review as well as the restriction to studies published in English or German. Then again, Pan et al. reported in their systematic review that foreign languages literature more

often consisted of general overviews rather than original reports 62 and the effect probably could also be mitigated by contacting experts.

Implications for clinical practice and future research

If costs are not prohibitive, for very selected cases of intractable nausea and vomiting unresponsive to any conventional antiemetic treatment/regimen, it might be worth considering off label use of NK1-antagonists as a last option, 26 entirely based on pathophysiological considerations and good evidence and safety profile in other indications. Ideally, those results should be published as a case report or a case series.

Additionally, NK1 antagonists are currently studied for a variety of indications including overactive bladder, pruritus and broad spectrum antitumor activity. 63, 64-66 This could produce at least weak evidence as a 'by-product'.

Conclusions

There is insufficient evidence for the use of NK1 antagonists for the management of nausea and vomiting in advanced disease. Nevertheless, evidence of effectiveness is needed to guide our clinical decision in this patient population. The three clinical examples of successful treatment of nausea, and the case report of vomiting in diabetic gastroparesis could help to formulate relevant research questions. Well designed multicenter trials 14 with good outcome measures, or n= 1 trials could be potential approaches for addressing these questions.

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