Nausea and vomiting

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Inhoudsopgave

Nausea and vomiting

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General

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The first version of the clinical practice guideline Nausea and vomiting was written in 1996 as part of the clinical practice guidelines for palliative care developed by the Comprehensive Cancer Centre Middle Netherlands. The guideline was revised in 2005 by A. de Graeff, M.B. Kuyper and G.M. Hesselmann and incorporated in the first edition of the guideline book by the Comprehensive Care Centres Netherlands. The guideline was again revised by A. de Graeff, C.M. Molenkamp and G.M. Hesselmann and the revised version was incorporated in the 2010 guideline book.
The current version was established in October 2013.

Objective

A guideline is a set of recommendations to support the most important clinical problems in daily medical practice. This guideline is based, as much as possible, on scientific research or consensus.

Target group

This guideline is intended for all professionals involved in the care of patients in the palliative phase who suffer from nausea and/or vomiting, such as general practitioners, nursing home physicians, medical specialists, nurses and dieticians.

Working method of the guideline development group

A new expert group was formed for the purpose of the current revision; a mandate was obtained from the relevant scientific and professional associations to this end (see appendix 1, appendix 2 and appendix 4).
Clinical questions were formulated at the start of the revision. These questions followed from an inventory of clinical problems collected in the field from professionals and patients (representatives). The three most relevant clinical problems(see appendix 5)were further developed into clinical questions (see appendix 6).

In the chapter Management and treatment - symptomatic treatment - pharmacological treatment, the clinical questions form the basis of the new consensus text based on literature research; the guideline development group members consulted and used the literature familiar to them, supplemented with the outcomes of an SMILE literature search (Short Methodological Inventarisation of Literature and Evidence) by the CCCN. Each clinical (sub)question was assigned to one or more guideline development group members. The literature was summarised by the group members during a literature discussion; this formed the basis of the conclusions. Recommendations that were subsequently made in order to answer the clinical questions were the result of conclusions from literature combined with other considerations (context in daily practice).

Aside from the consensus-based text, all the existing guideline text was revised by experts (updated text).

For more information

☐ Appendix 1 - Composition of the working group

Alle werkgroepleden zijn afgevaardigd namens een wetenschappelijke, beroeps- of patiëntenvereniging en hebben daarmee het mandaat voor hun inbreng (zie bijlage 2). Bij de samenstelling van de werkgroep is getracht rekening te houden met landelijke spreiding, inbreng van betrokkenen uit zowel academische als algemene ziekenhuizen/instellingen en vertegenwoordiging van de verschillende verenigingen/disciplines.

De patiëntenvereniging is eveneens vertegenwoordigd door middel van afvaardiging van de coördinator van de patiëntenvereniging, alsmede een ervaringsdeskundige vanuit de Nederlandse Leverpatiënten Vereniging.

De volgende instellingen en verenigingen zijn betrokken bij de revisie van de richtlijn:

- Nederlands Huisartsen Genootschap (NHG)
- Specialisten ouderengeneeskunde (Verenso)

- Nederlandse Vereniging van diëtisten (NVD)
- Verpleegkundigen en Verzorgenden Nederland (V&VN)
- Nederlandse Vereniging van Maag-Darm-Leverartsen (NVMDL)
- Palliactief
- Nederlandse Federatie van Kankerpatiëntenorganisaties (NFK)

De coördinatie, procesbegeleiding en de ondersteuning ligt bij IKNL (Integraal Kankercentrum Nederland).

☐ Appendix 2 - Members of the guideline development group

Name	Function	Workplace	Authorization
Dr. A. de Graeff, voorzitter	Internist-oncoloog Hospice-arts	UMCU, Utrecht Academisch Hospice Demeter, De Bilt	Palliactief
Mw. K.M. Duin	Diëtist	Medisch Centrum Alkmaar	NVD
Drs. H. Gerritsen	Huisarts	Zwolle	NHG
Mw. A. Guldemond	Verpleegkundig Specialist MANP	ZorgBrug, Gouda	V&VN PZ
Mw. A. Kennis	Diëtist	De Wever, Tilburg Instituut Verbeeten, Tilburg	NVD
Mw. drs. J.H.F. Leemhuis	Ervaringsdeskundige		NFK
Drs. P.H.G.M. Stadhouders	MDL-arts	Antonius Ziekenhuis, Nieuwegein	NVMDL
Drs. R.P.C. Westerink	Specialist Ouderengeneeskunde	IJsselheem, Kampen	Verenso
C. Laarakker	Ervaringsdeskundige		NFK
Mw. dr. M.J. Uitdehaag	Procesbegeleider/adviseur richtlijnen (eerste deel traject)	Groningen	IKNL
T. van Vegchel	Procesbegeleider/adviseur richtlijnen (tweede deel traject)	Amsterdam	IKNL
Mw. S. Janssen-van Dijk	Secretaresse	Rotterdam	IKNL

☐ Appendix 3 - Independence of guideline development group members

All working group members were asked to fill in a conflict of interest declaration, in which they stated their ties with the pharmaceutical industry at the start and completion of the guideline process.

☐ Appendix 4 - Involved and authorising associations

Initiative, organization and financing

IKNL (Integraal Kankercentrum Nederland)

Associations

- Nederlands Huisartsen Genootschap (NHG)
- Specialisten ouderengeneeskunde (Verenso)
- Nederlandse Vereniging van diëtisten (NVD)
- Verpleegkundigen en Verzorgenden Nederland (V&VN)
- Nederlandse Vereniging van Maag-Darm-Leverartsen (NVMDL)
- Palliactief
- Nederlandse Federatie van Kankerpatiëntenorganisaties (NFK)
- De coördinatie, procesbegeleiding en de ondersteuning ligt bij het Integraal Kankercentrum Nederland (IKNL).

Authorisation

- Specialisten ouderengeneeskunde (Verenso)
- Nederlandse Vereniging van diëtisten (NVD)
- Nederlandse Vereniging van Maag-Darm-Leverartsen (NVMDL)
- Palliactief
- Verpleegkundigen en Verzorgenden Nederland (V&VN)

Consenting associations

- Nederlands Huisartsen Genootschap (NHG)
- Nederlandse Federatie van Kankerpatiëntenorganisaties (NFK)

☐ Appendix 5 - Clinical problem inventory

Bijlage Clinical problem inventory (in dutch)

☐ Appendix 6 - Clinical questions

Nr.	Uitgangsvraag	Experts
1	Wordt de keuze van anti-emetica bij patiënten met misselijkheid en/of braken t.g.v. kanker, hartfalen, COPD, MS, ALS en nierfalen in de palliatieve fase bepaald door de oorzaak?	Dr. A. de Graeff
2	Wat is het effect van anti-emetica bij de behandeling van misselijkheid en/of braken bij de patiënt in de palliatieve fase met kanker, hartfalen, COPD, MS, ALS of nierfalen?	
	a. Metoclopramide vs domperidon	Drs. R.P.C. Westerink
	b. Haloperidol	Drs. H. Gerritsen
	c. Dexamethason	Mw. K.M. Duin en mw. M. Kennis
	d. Cyclizine	Dr. A. de Graeff
	e. Levomepromazine	Dr. A. de Graeff
	f. Olanzapine	Dr. A. de Graeff
	g. Serotonine-antagonisten	Dr. A. de Graeff
	h. Erythromycine	Drs. P.H.G.M. Stadhouders
	i. Cannabis	Drs. H. Gerritsen
	j. Gember	Drs. H. Gerritsen

3	Wat zijn de verschillen in effectiviteit en belasting tussen parenterale en rectale toediening van anti-emetica bij patiënten met misselijkheid en/of braken tgv kanker, hartfalen, COPD, MS, ALS of nierfalen in de palliatieve fase?	Drs. R.P.C. Westerink

Appendix 7 - Scientific argumentation

Elk hoofdstuk van de richtlijn bestaat uit een richtlijntekst. De teksten naar aanleiding van de uitgangsvragen zijn opgebouwd volgens het volgende vaste stramien: aanbevelingen, literatuurbespreking, conclusies en overwegingen. De antwoorden op de uitgangsvragen (derhalve de aanbevelingen in deze richtlijn) zijn voor zover mogelijk gebaseerd op gepubliceerd wetenschappelijk onderzoek.

Appendix 8 - Update

The period of validity of the guideline (maximum of 5 years) is being monitored by the IKNL programme office. For various reasons, it may be necessary to revise the guideline earlier than intended. Sections of the guideline will be amended in the interim, when required.

Appendix 9 - Guideline ownership

The owner of the guideline must be able to show that the guideline has been realised in a careful manner and using the required expertise. By owner, we are referring to the professional associations authorising the guideline. The IKNL takes care of managing and releasing the guideline.

Appendix 10 - Legal significance

The guideline contains recommendations of a general nature. It is possible that these recommendations are not applicable to an individual case. Facts or circumstances may in fact arise that require deviation from the guideline in the interest of the patient. When there is deviation from this guideline however, this must be substantiated in document format. The applicability and application of the guideline in the field is the responsibility of the treating physician.

Appendix 11 - Responsibility

The eight comprehensive cancer centres in the Netherlands promote access to integral and high-quality provision of care for people with cancer and their families. The comprehensive cancer centres have been established to improve treatment, care and clinical research within oncology. In addition, they are involved in setting up and supporting networks for palliative care.

Comprehensive cancer centres collaborate nationally within the IKNL on multidisciplinary development of guidelines for oncological and palliative care. Aside from development of guidelines, the comprehensive cancer centres also facilitate maintenance, management, implementation and evaluation of these guidelines. The framework for development of the guidelines for oncological and palliative care is the AGREE instrument. This instrument was created for evaluation of existing, new and revised guidelines.
The AGREE Instrument evaluates both the quality of the reports and the quality of particular aspects of the recommendations. It evaluates the likelihood that a guideline will achieve its objective, but not the actual impact on patient outcomes.

The AGREE Instrument consists of 23 items organised in six domains. Each domain covers a separate dimension of guideline quality, namely:

- **Scope and goal** is concerned with the overall aim of the guideline, the specific clinical questions answered by the guideline and the target patient population.
- **Stakeholder involvement** focuses on the extent to which the guideline represents the views of its intended

users.
- **Methodology** relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations and to update them.
- **Clarity and presentation** deals with the language and format of the guideline.
- **Applicability** pertains to the likely organisational, behavioural and financial implications of applying the guideline.
- **Editorial independence** is concerned with the independence of the recommendations and acknowledgement of possible conflict of interest from the guideline working group.

Appendix 12 - Implementation

Een veel gebruikte definitie omschrijft implementatie als ‘een procesmatige en planmatige invoering van vernieuwingen en/of verbeteringen (van bewezen waarde) met als doel dat deze een structurele plaats krijgen in het (beroepsmatig) handelen, in het functioneren van organisatie(s) of in de structuur van de gezondheidszorg'. In deze definitie is verspreiding slechts één onderdeel, het startschot van een bredere implementatiestrategie. Een noodzakelijke, maar geen voldoende voorwaarde voor gedragsverandering.

Het bevorderen van het gebruik van de richtlijn Misselijkheid en braken begint met een brede verspreiding van de richtlijn. Er wordt een mailing verstuurd naar de professionals via de (wetenschappelijke) verenigingen en de werkgroepen van IKNL. Ook is de richtlijn gepubliceerd op pallialine en www.richtlijnendatabase.nl. In verschillende tijdschriften of bij bijvoorbeeld nascholingsbijeenkomsten wordt de richtlijn onder de aandacht gebracht. Om het gebruik in de dagelijkse praktijk te bevorderen is er een samenvattingskaart en een Engelse vertaling van de richtlijn gemaakt. Daarnaast beschikt IKNL over een toolbox ter ondersteuning van de IKNL adviseurs netwerken c.q. professionals in het veld voor de implementatie van de richtlijn. De toolbox bevat:

- een overzicht van de aanbevelingen
- de kernboodschappen (belangrijkste inhoudelijke boodschappen)
- een basis PowerPoint presentatie voor IKNL adviseurs netwerken en werkgroepleden van deze richtlijn
- een implementatieplan voor deze richtlijn. Dit plan bevat voor de belangrijkste aanbevelingen uit de richtlijn een overzicht van belemmerende en bevorderende factoren voor de implementatie. Op basis hiervan beschrijft het plan de belangrijkste doelgroepen en (adviezen voor) concrete acties om implementatie te bevorderen
- een training aan de IKNL adviseurs netwerken

Introduction

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Introduction

Nausea is a subjective sensation that is difficult to define. It is an unpleasant feeling in the abdomen, often associated with the sense of being ill, a lack of appetite and the urge to vomit.
Early satiety is the feeling of fullness after ingesting a small amount of food or drink.
Vomiting is the forcible expulsion of stomach contents through the mouth.
Retching is a strong, belching-like, rhythmic movement in the oesophagus without vomiting.
Regurgitation is the passive return of gastric contents to the oesophagus and potentially the mouth; this is not associated with nausea.

Nausea and vomiting often (but not always) occur in combination.
Nausea and/or vomiting may be accompanied by salivary discharge, pallor, sweating, tachycardia, and the urge to defaecate.

Nausea and/or vomiting have a highly negative effect on quality of life. Persistent symptoms of nausea and/or vomiting may lead to a reduced intake of food and fluids and ultimately to dehydration, metabolic dysfunction (impaired renal function, hypokalaemia, metabolic alkalosis), malnutrition, exhaustion, haematemesis caused by oesophageal lacerations (Mallory-Weiss syndrome) or aspiration pneumonia. It may also lead to being unable or unwilling to take medication, and discontinuation of radiotherapy or chemotherapy.

Prevelance

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Nausea occurs in 31% and vomiting in 20% of patients with an advanced stage of cancer. In addition, a lack of appetite (53%) and early satiety (23%) are relatively common. Nausea occurs in 25% of patients with heart failure and in 4% of patients with chronic obstructive pulmonary disease (COPD) in the last year before dying.

The prevalence depends greatly on gender, age, underlying disease and disease stage. Nausea and/or vomiting occur more frequently in female and younger cancer patients, and in those cancer patients that have a strong tendency to experience motion sickness or sea sickness. Nausea and/or vomiting are more common in patients with breast cancer, gynaecological tumours, pancreas or gastric cancer (especially in the presence of peritonitis carcinomatosa or obstruction) and relatively less common in patients with bronchial carcinoma and brain tumours.

Complaints of nausea and/or vomiting occur in 10-50% of patients using opioids, especially in the first week of treatment or the first days after an increase in dose.

Pathophysiology

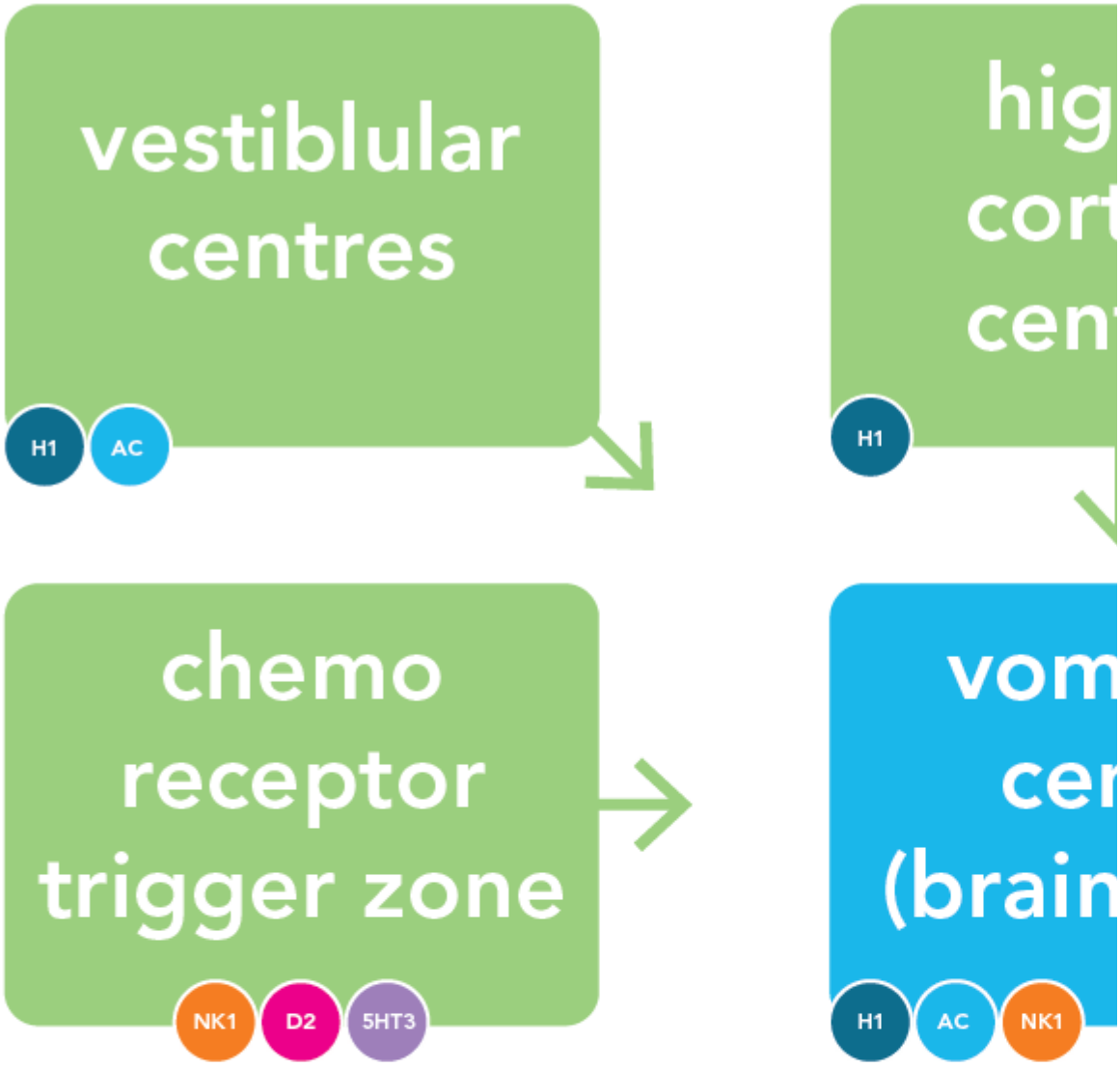
Vastgesteld: 16-06-2014 Regiehouder: IKNL

The nausea and vomiting response is regulated by the vomiting centre (the nucleus of the solitary tract and dorsal nucleus of the vagus nerve), which is found in the brain stem (see Figure 1). The various neurotransmitters and receptors involved in the regulation are: dopamine-2 (dopamine or D2 receptor), serotonin (serotonin or 5HT3 receptor), acetylcholine (acetylcholine or muscarinic receptor), histamine (histamine or H1 receptor), substance P (neurokinin-1 or NK1 receptor) and gamma-aminobutyric acid (gamma-aminobutyric acid (GABA) receptor).

The most important afferent routes for these factors derive from:

- the vagus nerve
- the chemoreceptor trigger zone, which is also located in the brain stem (area postrema), but outside the blood-brain barrier
- the labyrinth
- higher cortical centres

Peripheral stimulation of chemo- and mechanoreceptors in the stomach, intestine, and peritoneum activate the vomiting centre via the vagus nerve. Stimulation of the vomiting centre is induced by receptors in the chemoreceptor trigger zone, which are activated by medications and metabolic disorders (e.g. hypercalcaemia or renal insufficiency). Vestibular and cerebral/psychogenic factors affect the vomiting centre by means of the afferent routes from the labyrinth and the cortical centres, respectively.



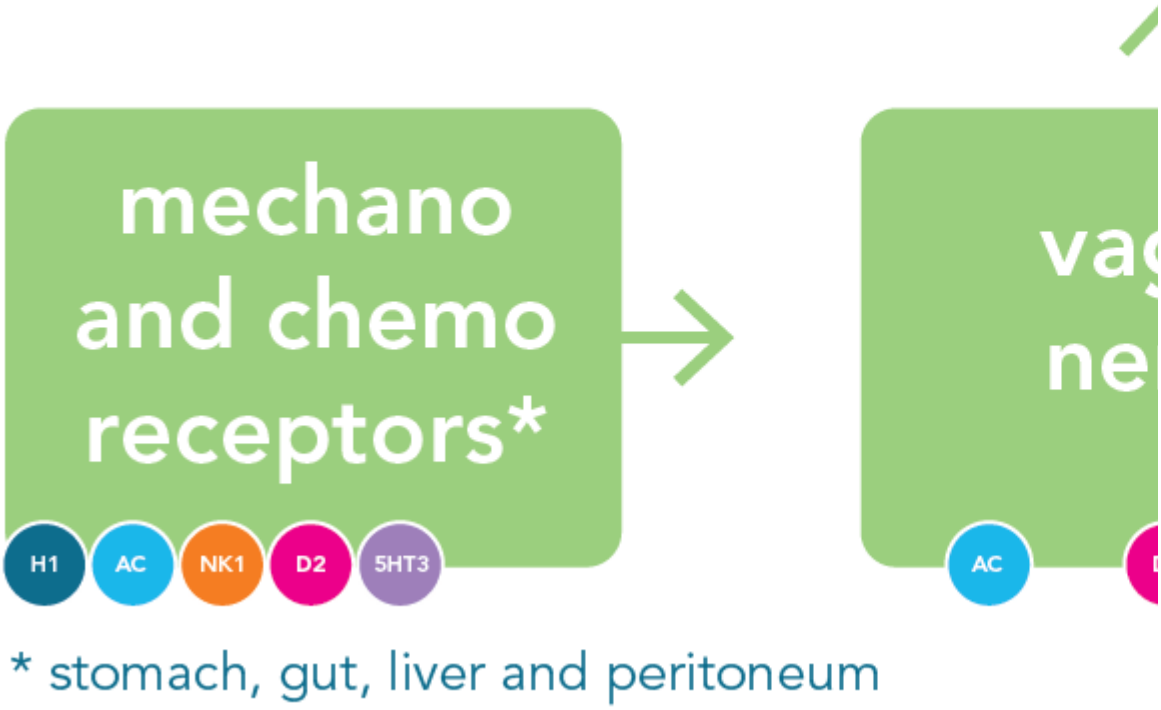


Figure 1. Pathophysiology of nausea and/or vomiting
H1 = histamine receptor; AC = acetylcholine receptor; NK1 = neurokinin-1 receptor;
D2 = dopamine-2 receptor; 5HT2/3 = serotonin receptors. GABA = gamma-aminobutyric acid receptor

The vomiting centre stimulates the diaphragm (via the phrenic nerve), the striated muscle tissue of the abdominal wall and thorax (via the spinal nerves), and the muscle tissue of the stomach, oesophagus, larynx, and pharynx (via the vagus nerve). This stimulation produces the retching sensation and/or vomiting and accompanying symptoms.

Prokinetic drugs (metoclopramide, domperidone) promote gastric emptying by blocking D2 receptors in the gastric wall; additionally, metoclopramide activates receptors in the gastric wall, which leads to release of acetylcholine, which in turn further promotes gastric emptying.

Aetiology

Vastgesteld: 16-06-2014 Regiehouder: IKNL

There are several causes of nausea and/or vomiting, which may occur simultaneously and have reciprocal enhancing effects. Multiple causative factors are evident in 25% of cases. A clear cause cannot be found in 25-33% of cases.

Known causes include the following:

1. Delayed gastric emptying (35 - 44%)
    - gastroparesis as a result of abnormal gastric motor function:
        - tumour invasion (gastric carcinoma, metastasis from elsewhere)
        - after partial or total gastrectomy
        - as part of the anorexia-cachexia syndrome
        - paraneoplastic autonomic neuropathy
        - medication (including opioids, anticholinergic agents, vinca alkaloids, cisplatin, calcium blockers)
        - comorbidity (e.g. diabetes mellitus, renal failure, amyloidosis, scleroderma)
    - decreased gastric capacity caused by gastric carcinoma or compression due to hepatomegaly, extragastric tumours or ascites
    - pyloric or duodenal obstruction, e.g. as a result of a pancreatic carcinoma
    - gastritis or ulcer
        - peptic
        - drug-related: aspirin, NSAIDs, dexamethasone, mucolytic agents, antibiotics, iron preparations
        - radiotherapy of the spine or stomach in which the stomach lies within the radiation field
2. Other abdominal causes (24-32%)
    - constipation
    - infiltration or traction of the mesenterium or peritoneum caused by carcinomatous peritonitis (with or without ascites)
    - ileus (due to obstruction, pseudo-obstruction, adhesions, faecal impaction, acute bacterial peritonitis or sepsis)
    - liver metastases (caused by hepatomegaly and/or metabolic abnormalities or icterus)
    - congested liver associated with heart failure
    - reflux
    - dumping syndrome after gastric resection
    - gastroenteritis, pancreatitis, cholecystitis, cholangitis, hepatitis, cystitis
    - gall stones, kidney stones
    - recent surgery
    - cough or hiccups leading to reflectory vomiting
3. Chemical/metabolic causes (30-33%)
    - medications:
        - opioids (especially shortly after starting or after a dose increase)
          These agents may cause nausea and/or vomiting via different mechanisms: activation of the chemoreceptor trigger zone, delayed gastric emptying (see point 1) and vestibular (see point 5)
        - chemotherapeutic agents
          Nausea and/or vomiting can be acute (within 24 hours after administration) or delayed (more than 24 hours after administration); it is likely that different mechanisms play a role .
        - The incidence of nausea and vomiting is highly dependent on the dose and type of chemotherapeutic agents used. A distinction is made between highly emetogenic chemotherapy (>90% chance of vomiting without anti-emetics), moderately emetogenic chemotherapy (30-60%) and low or not emetogenic chemotherapy (<30%).
          Other factors that may increase the chance of nausea and/or vomiting occurring after

chemotherapy are: female gender, young age, sensitivity to nausea (e.g. during pregnancy or in the case of motion sickness or sea sickness), fear/stress and prior poor experiences with chemotherapy
        - tyrosine kinase inhibitors (including sunitinib, sorafenib, imatinib, erlotinib)
        - other medications (including anti-epileptic agents, theophylline, digoxin, SSRIs, anaesthetics)
    - electrolyte disorders (hypercalcaemia and hyponatraemia)
    - acute or chronic renal insufficiency
    - liver failure
    - dysregulated diabetes mellitus
    - bacterial toxins and sepsis
4. Cerebral/psychogenic causes (7%)
    - brain metastases or primary brain tumour with increased intracranial pressure
    - leptomeningeal metastases
    - meningitis (infectious, chemical)
    - stroke
    - total cranial irradiation
    - influences relating to smell and taste
    - severe pain
    - anxiety and stress
    - **anticipatory nausea and vomiting:** through classical conditioning, stimuli associated with the original stimulus by means of time or place (e.g. chemotherapy) can induce nausea or vomiting
5. Vestibulary causes (very rare in the palliative phase):
    - pharmacological (opioids, aspirin)
    - labyrinth disorders: motion sickness, Ménière's disease, neuritis vestibularis or labyrinthitis
    - tumour of the inner or middle ear/base of skull

Diagnostics

Vastgesteld: 16-06-2014 Regiehouder: IKNL

This chapter is subdivided into subchapters and/or sections. To view the content, click on the subchapter and/or section title in the left-hand column.

Patient history

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Patient history

- medical history, earlier experience or periods with nausea and/or vomiting, (change of) medication (including medical self-care), recent chemo- or radiotherapy
- presence, duration, course, and severity of nausea
- presence, frequency, course and severity of retching and/or vomiting; amount of vomit; characteristics and odour; presence of food remnants and/or blood in vomit; relation to mealtimes and the nature of the food
- relationship between nausea and vomiting; improvement in nausea after vomiting
- triggering factors (meals, type of food, posture or movement, specific smell or environment)
- effective intake of food and fluids, changes in weight
- use of antiemetics and the effects of these medications
- concomitant complaints, such as: anorexia, difficulty swallowing or digesting, early satiety, burping, acid burn, regurgitation, abdominal pain or cramps, swollen abdomen, stomach rumbling, flatulence, constipation or diarrhoea, thirst, polyuria, pain (other than abdominal pain or headache), coughing, hiccups, dizziness, hearing impairment, neurological complaints, shortness of breath
- anxiety, stress, depression, and their effect on symptoms

The history may provide important information regarding the cause of nausea and/or vomiting:

- early satiety, small amounts of vomit with varying degrees of nausea may indicate gastroparesis
- severe vomiting with food remnants directly after meals, resulting in rapid dehydration, indicates a pyloric or duodenal obstruction
- small amounts of vomit with no signs of gastric retention are consistent with decreased gastric capacity, caused by a tumour or external compression
- vomiting combined with increased abdominal girth and shortness of breath can indicate ascites
- position-dependent nausea and/or vomiting may be caused by fluid stasis in the stomach, infiltration of the mesenterium/peritoneum, or hypersensitivity of the vestibular apparatus (with neuritis vestibularis; as a rare side effect of opioids or as a result of a tumour of the inner or middle ear)
- vomiting (in the morning), (often without nausea; sometimes explosive), combined with a headache and/or neurological defects, indicates increased intracranial pressure in the case of, for example, a brain tumour or brain metastasis, leptomeningeal metastases or stroke
- vomiting combined with thirst, polyuria, constipation, drowsiness, and/or confusion may indicate hypercalcaemia or other electrolyte disorders
- vomiting and/or vomiting related to a particular sensation or association indicate a psychogenic cause

It is recommended (as long as the nausea and/or vomiting is not under control) that the patient scores his nausea and/or vomiting 1-2 times per day, for example, with a score on a scale of 0 to 10, in which 0 indicates the absence of nausea or vomiting and 10 the constant presence of intolerable nausea or vomiting. The Edmonton Symptom Assesment Scale (ESAS) may be used for this purpose.

Physical Examination

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Physical examination

- general: nutritional status, weight, hydration status, icterus, drowsiness, mood
- inspection of the mouth and pharynx (especially candidiasis)
- abdominal examination: surgical scars, herniation, peristalsis (absence of peristalsis and/or gurgling sounds in the case of ileus), signs of ascites (shifting dullness = position-dependent dullness during percussion, undulation = fluid wave induction in the flanks), distended stomach (clapotage = sloshing sound when the gastric region is pressed), liver enlargement, abnormal resistance, pain when pressure is applied, faecal impaction on rectal examination
- fundoscopy/neurological examination if increased intracranial pressure or overstimulation of the vestibular system is suspected

Inspection of the vomit may provide additional information. Large amounts of food remnants indicate pyloric or duodenal obstruction or bowel obstruction. Faecal-smelling vomit indicates obstruction of the small intestines.

Additional Tests/Examination

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Additional tests/examination

If required, additional tests may be performed as indicated:

- blood tests:
  - to determine the degree of dehydration, renal impairment, and/or potassium loss: serum urea, serum creatinine, serum potassium
  - to determine hypercalcaemia:
    - total calcium: in the case of low serum albumin, correct using the formula: **corrected Ca = serum calcium + 1.0 - (0.025 x serum albumin)**
    - or Ca2+ (correction for low serum albumin not necessary)
  - if hyponatraemia is suspected: serum sodium
  - with dysregulated diabetes mellitus: glucose
- urine analysis if cystitis is suspected
- diagnostic imaging:
  - if constipation or ileus is suspected: abdominal X-ray, CT scan of the abdomen, X-ray of small intestines using gastrographin
  - if gastric or duodenal obstruction, liver metastases, ascites, or peritonitis carcinomatous is suspected: abdominal ultrasound or CT scan
  - if neurological causes are suspected: brain MRI, possibly CT scan with contrast, lumbar puncture
- if gastritis, ulcer, tumour, or gastric or duodenal compression or obstruction is suspected: gastroscopy

Mangement and treatment

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Symptom scores for nausea and vomiting or the Utrecht Symptom Diary may be used to evaluate the effect of treatment (see appendix). Scoring the nausea and vomiting in this manner provides insight into the progression of symptoms and the effect of interventions.
At the start of treatment, management should be evaluated at least once per day by a nurse and/or physician.

This chapter is subdivided into subchapters and/or sections. To view the content, click on the subchapter and/or section title in the left-hand column

Integral approach

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Patient information

- Provide information regarding the possible causes of nausea and vomiting, relevant factors, and the expected duration, in language that is easy for the patient to understand. The potential risks, symptoms, consequences and risks of dehydration should also be mentioned. Check if the patient has understood the information
- Provide information regarding the objective, effect, possible side effects of treatment with antiemetics and taking antiemetics correctly
- Explain when the treatment is expected to have an effect and the factors that may lead to adjustment of the treatment
- Provide information regarding the (non-)administration of parenteral fluids (see the guideline Dehydration)

Communication

- Ascertain whether the patient is experiencing anxiety, (existential) stress or other psychogenic factors
- Discuss the change in role of nutrition and its importance in relation to the prognosis with the patient and his/her family and possible changes thereof.
- Discuss the use and benefit of the ESAS.

Supportive care

- Ascertain whether advice from a dietician is needed to prevent unnecessary deterioration in nutritional status or to discuss the role of nutrition in relation to complaints
- Discuss the influence of relaxation and distraction in situations in which anxiety plays a role. If required, contact a physiotherapist (for relaxation and massage), psychologist (relaxation, hypnosis, cognitive behavioural therapy for anticipatory nausea and vomiting), music therapist (relaxation and distraction), social worker (if there are financial or social issues) or spiritual care provider
- Consider pharmacological support with anxiolytics for anxiety and stress
- Consider engaging a volunteer in the terminal phase if the care threatens to become too much for the family.

Continuity of care

- Ensure multidisciplinary collaboration and effective patient transfer amongst care providers
- Formulate and individual care plan

Treating the cause

Vastgesteld: 16-06-2014 Regiehouder: IKNL

- Targeted antitumour therapy (surgery, radiotherapy, or chemotherapy) should be employed only if there is a reasonable chance of response and a low risk of (severe) side effects
- Dose modification or, if necessary, discontinuation; in the case of opioids as cause: consider opioid rotation if complaints persist or try an alternative route of administration
- In the case of obstruction of the gastric outlet or duodenum and a life expectancy of several weeks or longer, stent placement may be considered. In >80% of cases, this results in a temporary or permanent reduction of the symptoms or the symptoms disappear completely. Possible complications are obstruction of the stent (18%), migration (5%) and bleeding and/or perforation (1%). A bypass operation (gastrojejunostomy) is rarely indicated
- Treatment of constipation, pain or cough
- Treatment of reflux, peptic ulcer, gastritis, gastroenteritis, pancreatitis, cholelithiasis, nephrolithiasis or cystitis
- Treatment of electrolyte disorders:
    - hypercalcaemia: zoledronic acid 4 mg i.v. or APD 90 mg i.v. + 3 - 4 litres of 0.9% NaCl/24 hours; this often implies hospital admission for fluid administration and frequent blood samples
    - hyponatraemia: water restriction (for SIADH) or broth/0.9% NaCl i.v. or s.c. (if there is concurrent dehydration)
- With ascites: consider ascites puncture or (in the case of transudate) diuretics
- With ileus:
    - discuss the feasibility and desirability of surgery with the surgeon
    - if surgery is not an option, use conservative therapy:
        - drainage of gastric contents (nasogastric tube) as needed during the acute phase (particularly for severe vomiting)
        - somatostatin analogues: octreotide 100 - 300 microgram s.c. three times daily or 300 - 900 microgram/24 hours continuous s.c. or i.v. infusion (particularly for severe vomiting); or, during the stable phase after the efficacy of octreotide has been confirmed, octreotide LAR 30 mg i.m. once every 4 weeks/lanreotide PR 30 mg i.m. once every 2 weeks
        - hyoscine butylbromide 40 - 120 mg/24 hours s.c. or i.v.
        - in the case of persistent nausea and vomiting despite pharmacological treatment: continuous gastric drainage with the use of a nasogastric tube or via existing percutaneous endoscopic gastrostomy (PEG) tube
- With brain metastasis: corticosteroids (dexamethasone 4 mg/day orally, s.c., or i.v.; if necessary higher doses can be given) and possibly radiotherapy or resection

Symptomatic management: non-pharmacological

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Nutritional advice

Recommend the following to the patient:

- eat what he/she tolerates well and appreciates the taste of
- use frequently small meals and snacks to prevent an empty stomach (if there is no gastric retention)
- consider cold meals, if the aroma of food leads to complaints
- use meals and snacks at moments that the complaints are less intense; take advantage of good moments
- take sufficient fluids (at least 1.5 l/day)
- consider drinking cola (carbonated or uncarbonated)
- consider sucking on an ice cube or popsicle pieces of frozen/cooled fruit sometimes works well
- consider dietary supplements, if maintaining or improving nutritional status is desired. Consulting a dietician is essential for this.

Lifestyle advice

Recommend the following to the patient:

- sit in an upright position for 30 - 45 minutes after eating
- maintain a quiet environment and fresh air
- practice good oral hygiene and care
- make sure there is a container and enough tissues and water to rinse the mouth

Advise the patient to avoid:

- the smell and sight of food, if this leads to complaints. Remove food immediately if it has not/will not be used
- fatty, very spicy, too hot or too strongly smelling meals
- cold drinks
- constricting clothing
- strong perfume

Administration of fluids and electrolytes

If there are indications of (threatening) dehydration based on the patient history, physical examination and any laboratory analysis, parenteral fluid administration can be considered, depending on the life expectancy and the wishes of the patient. In the case of hypokalaemia, supplemental potassium may be given intravenously.

Gastric drainage

Gastric drainage may be considered if there is severe vomiting as a result of a total obstruction of the pylorus or the duodenum, an ileus or an untreatable gastroparesis. In these situations, a nasogastric or existing PEG tube can be used to drain stomach contents, thereby preventing vomiting.

Acupuncture and acupressure

There are indications that acupuncture and/or acupressure (in the form of pressure massage or a special wristband) are effective in the case of nausea and/or vomiting, particularly after surgery and after chemotherapy.

Complementary forms of care and psychological techniques

Complementary forms of care and psychological techniques are used to manage nausea and/or vomiting primarily when psychogenic factors (anxiety and stress) and conditioning (with anticipatory nausea and/or vomiting) play an important role. These types of nausea and/or vomiting respond poorly to antiemetics. These techniques act through relaxation, distraction, and/or a feeling of self-control. In first instance, instruction from a physiotherapist or psychologist is necessary. In most cases, a physician, nurse, or even the patient can generally apply the technique

on their own after this.
The techniques listed below have primarily been researched with nausea and/or vomiting resulting from chemotherapy:

- massage of feet, hands or the face
- aromatherapy (alone or in combination with massage)
- relaxation exercises (progressive muscle relation), alone or with guided fantasy exercises
- listening to music

The approach used must be tailored to the patient. Some patients will benefit more from a physical approach aimed at relaxation, while others may respond to a more active approach involving behavioural therapy.

Symptomatic management: pharmacological

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Introduction

Antiemetics have different methods of action (see Table 1). Some agents have multiple mechanisms of action and interact with various receptors.
The following agents are used as antiemetics (see Table 2):

- dopamine antagonists (metoclopramide, domperidone, haloperidol)
- prokinetic drugs (metoclopramide, domperidone): promote gastric emptying by inhibiting dopamine receptors in the stomach and (only in the case of metoclopramide) stimulate cholinergic receptors in the stomach
- serotonin (5HT3) antagonists (ondansetron, granisetron, tropisetron, palonosetron)
- neurokinin-1 antagonists (aprepitant, fosaprepitant)
- corticosteroids (in practice especially dexamethasone, method of action unknown)
- anticholinergic agents (scopolamine, hysocine butylbromide)
- levomepromazine, olanzapine: antidopaminergic as well as antiserotonergic (5HT2), anticholinergic and antihistaminergic mode of action
- antisecretory agents: octreotide/lanreotide (somatostatin analogues: a gastrointestinal hormone that inhibits secretion in the gastrointestinal tract)

There is a chance with a number of the abovementioned agents (scopolamine, levomepromazine and olanzapine) of anticholinergic side-effects, such as a delirium. This is especially the case with elderly patients. Metoclopramide and haloperidol have extrapyramidal disorders, akathisia, dystonia and drowsiness as possible side-effects and are contraindicated in patients with Parkinson's disease.
Antiemetics may be administered by oral, rectal, transdermal, or parenteral (subcutaneous or intravenous) routes.

Table 1. The mechanism of action of antiemetics

	Central dopamine-antagonist	5-HT3-antagonist	5-HT2-antagonist	Pro-kinetic agent	Anti-cholinergic agent	Anti-histaminic agent	Neurokinin-1 antagonist
Metoclopramide	++	+		++			
Domperidon	++			++			
Haloperidol	++				+		
Ondansetron, granisetron, tropisetron, palonosetron		++					
Corticosteroids[1]							
Scopolamine\ Hyoscine butylbromide					++		
Levomepromazine, olanzapine	++		++		++	++	
Aprepitant, fosaprepitant							++

[1] Mechanism of antiemetic action unknown

Tabel 2. Antiemetics

Agent/ method of administration	Mechanism of action	Dose	Dose
Metoclopramide Tablet, drink, suppository, injection	Central dopamine-2 antagonist Prokinetic agent(advances gastric emptying) Weak serotonin(5HT3) antagonist	3 dd 10 mg orally or supp. In case of insufficient effect, high doses (40-100 mg/24 hrs s.c. or i.v.) can be considered	May worsen colic-like abdominal pain if there is ileus Do not combine with anticholinergic agents Central side effects: extrapyramidal side effects, akathisia, dystonia, drowsiness, especially at an elderly age and/or with comedication
Domperidon Tablet, suspension, suppository	Central dopamine-2 antagonist Prokinetic agent	3-4 dd 10-20 mg orally 3-4 dd 60-120 mg supp	May worsen colic-like abdominal pain if there is ileus Do not combine with anticholinergic agents Few or no central side effects. Arrhythmia
Haloperidol Tablet, drops (buccal), injection	Dopamine-2 antagonist (central)	2 dd 1-2 mg orally 2 dd 0.5-1 mg s.c. or i.v., or 1-2 mg/24 hrs s.c. or i.v. Dose orally. : s.c./i.v. = 2 : 1	Side effects: extrapyramidal side effect, akathisia, dystonia, drowsiness, dry mouth, vision abnormalities, urine retention, arrhythmia
Dexamethasone Tablet, drink, injection	Reduction in cerebral oedema and possibly also oedema around the tumour or metastasis Other mechanisms unknown	1 dd 4-8 mg orally, s.c. or i.v. Dose orally = s.c./i.v..	Especially with chemotherapy (acute and delayed nausea and vomiting) or increased intracranial pressure With therapy-resistant nausea and/or vomiting
Ondansetron Tablet, orodispersible tablet, syrup, suppository, injection	Serotonin (5HT3) antagonist (central + peripheral)	1-2 dd 8 mg orally or i.v. 1 dd 16 mg supp. 16mg/24 hrs s.c. or i.v.	Especially with chemotherapy or radiotherapy, postoperative or with nausea and vomiting as a result of renal failure. Constipation as a side effect
Granisetron Tablet, injection, patch	Serotonin (5HT3) antagonist (central + peripheral)	2 dd 1 mg orally 1-3 dd 3 mg i.v. 3.1 mg/24 hr transdermal	Especially with chemotherapy, radiotherapy or postoperative Granisetron transdermal in the case of treatment across multiple days Constipation as side effect
Tropisetron Tablet, injection	Serotonin (5HT3) antagonist (central + peripheral)	1 dd 5 mg orally or i.v.	Especially with chemotherapy or radiotherapy or postoperative Constipation as side effect

Agent/ method of administration	Mechanism of action	Dose	Dose
Palonosetron	Serotonin (5HT3) antagonist (central + peripheral)	250 µg i.v. (single dose)	With chemotherapy Constipation as side effect
Aprepitant Capsule	Neurokinin-1 (NK1) antagonist	1 dd 125 mg orally on day 1 1 dd 80 mg orally on day 2-3	With nausea and/or vomiting as a result of chemotherapy Increases levels of dexamethasone
Fosaprepitant, injection	Neurokinin-1 (NK1) antagonist	1 dd 150 mg i.v. on day 1	
Levomepromazine Tablet, injection	Dopamine-2 antagonist 5-HT2 antagonist Antihistaminic agent Anticholinergic agent	Starting dose 1 dd 6.25-12.5 mg orally a.n. or 3.12 mg s.c. (as bolus or as continuous infusion), increase where necessary to max. 25 mg dd Dose orally : s.c. = 2 : 1	Sedation, dry mouth Can also be administered buccally As monotherapy with therapy-resistant nausea and/or vomiting Is not reimbursed
Olanzapine Tablet, injection	Dopamine-1/4 antagonist Serotonin (5HT2,3,6) antagonist Antihistaminic agent Anticholinergic agent	1-2 dd 5 mg orally	Increased chance of CVA and death reported for use in elderly patients with dementia
Scopolamine	Anticholinergic agent	1-2 patches of 1.5 mg every 3 days	Place behind the ear Side effects: dry mouth, vision disturbances, urine retention, confusion. Do not combine with prokinetic agents
Scololaminebutyl Injection	Anticholinergic agent	40-120 mg/24 hrs s.c. or i.v.	With ileus Dry mouth, impaired vision, urine retention, confusion Do not combine with prokinetic agents. .

Agent/ method of administration	Mechanism of action	Dose	Dose
Cyclizin Tablet, suppository	Antisecretory agent	50 mg orally 3-4 times daily 100 mg rectally 3 times daily	Do not combine with prokinetic drugs Reimbursement only with prescription for chronic use
Octreotide Injection	Antisecretory agent	3 dd 100-300 microgr or 300-900 microgr/24 h s.c. or i.v.	With ileus
Octreotide LAR Injection	Antisecretory agent	30 mg i.m. once every 4 weeks	With ileus, responding well to octreotide
Lanreotide PR Injection	Antisecretory agent	30 mg i.m. once every 4 weeks	With ileus, responding well to octreotide

Almost all research on the effect of antiemetics has been performed in cancer patients. In making the recommendations given below, no distinction is made between cancer patients and patients with other life-threatening disorders.

For patients in the palliative phase of nausea and vomiting as a result of other causes than chemotherapy, ileus, brain metastases, terminal renal failure or vestibular causes, it is recommended to choose an empirical approach with metoclopramide as first choice. In case of (a high risk of) central side effects that (may) bother the patient, the use of domperidone is preferred (see paragraph effectiveness of antiemetics on the basis of the cause and effect of metoclopramide and domperidone).

Haloperidol is recommended for the treatment of nausea and vomiting in the palliative phase as alternative for metoclopramide or domperidone, especially if there is another indication for this agent (such as hallucinations or (starting) delirium) (see paragraph effect of haloperidol).

The guideline development group is of the opinion that dexamethasone monotherapy may be employed in the treatment of nausea and vomiting in the palliative phase if there is insufficient response to treatment with metoclopramide, domperidone or haloperidol (see paragraph effect of dexamethasone).

Treatment with levomepromazine orally (possibly buccally or s.c.) is recommended for patients in the palliative phase with nausea and/or vomiting that responds insufficiently to other antiemetics. Olanzapine is an alternative (see paragraph effect of levomepromazine and olanzapine).

Treatment with serotonin antagonists is recommended for patients in the palliative phase:

- to prevent or treat nausea and vomiting as a result of chemotherapy, radiotherapy or postoperatively
- with nausea and/or vomiting that does not respond sufficiently to earlier treatment with metoclopramide, domperidone, haloperidol, dexamethasone and levomepromazine
- as a first choice in patients with terminal renal failure with nausea and vomiting
  see paragraph effect of serotonine-antagonists).

Due to a lack of research and clinical experience, no recommendations are made about the use of cyclizine in the treatment of nausea and vomiting in patients in the palliative phase (see paragraph effect of cyclizine).

Erythromycin is not recommended for the treatment of nausea or vomiting for patients in the palliative phase, unless there is gastroparesis with diabetes mellitus or after vagotomy (see paragraph effect of erythromycin).

Ginger is not recommended for patients in the palliative phase with nausea and/or vomiting (see paragraph effect of ginger).

In some cases, the choice of agents is dependent on the cause of the nausea and/or vomiting:

- prokinetic drugs (metoclopramide or domperidone) with gastroparesis
- serotonin (5HT3) antagonists (possibly in combination with dexamethasone and (fos)aprepitant) with nausea and/or vomiting postoperatively or after radiotherapy, to prevent or treat nausea and vomiting as a result of chemotherapy (only during the first 24 hours) or nausea and/or vomiting with terminal renal failure
- aprepitant to prevent nausea and/or vomiting after highly emetogenic chemotherapy
- dexamethasone if there is nausea due to chemotherapy (in combination with serotonin antagonists), in the case of brain metastases with oedema and possible with ileus
- scopolamine patch for vestibular causes of nausea and/or vomiting
- octreotide/octreotide LAR/lanreotide and/or hyoscine butylbromide for pharmacological treatment of ileus

In all other cases an empirical approach is chosen, in which metoclopramide or domperidone are started (usually orally or rectally), independent of the cause of the nausea and/or vomiting. A switch is made from metoclopramide to domperidone if there are central side effects. It is also possible to choose haloperidol, especially if there is another indication to do so (hallucinations or (starting) delirium).
The effect of oral or rectal administration of metoclopramide and domperidone can be assessed within 1-2 hours, the effect of oral administration of haloperidol after 2-6 hours.

Given that metoclopramide and haloperidol are both dopamine antagonists, combining these agents for the treatment of nausea is not rational. Moreover, the chance of extrapyramidal side effects when combining these agents increases greatly. If adequately dosed metoclopramide or domperidone does not provide sufficient effect, it is not rational to switch to haloperidol. Metoclopramide and domperidone must not be combined with agents with anticholinergic (side-)effects because they counteract the prokinetic effect.
If metoclopramide, domperidone or haloperidol has insufficient effect, these agents are discontinued and the patient is started on dexamethasone 1 dd 4-8 mg orally. The effect of this can only be assessed after 24-48 hours.

A switch is made to levomepromazine if the effect is insufficient. Olanzapine or serotonin antagonists (ondansetron, granisetron or tropisetron) are possible alternatives. If there is persistent vomiting, rectal administration of metoclopramide or domperidone is chosen, or parenteral administration of:

- metoclopramide: 40-100 mg/24 hours s.c. or i.v. as continuous infusion
- haloperidol: 1-2 mg s.c. or i.v. twice daily or 2-4 mg/24 hours s.c. or i.v. as continuous infusion
- dexamethasone: once daily 4-8 mg s.c. or i.v.
- ondansetron: 8 mg twice daily or 16 mg/24 hours s.c. or i.v.
- levomepromazine: 3.25-12.5 mg s.c. a.n. or as continuous infusion

With the exception of dexamethasone, the aforementioned agents may be easily combined with other agents (e.g. morphine) in one solution. The disadvantages of this approach, however, are that the dose of each agent can no longer be adjusted individually and a bolus injection is not wellr possible.

In relation to the choice between rectal and parenteral administration of antiemetics, the following recommendation has been made on the basis of the detailing for clinical question 3:

- When making a choice between rectal or parenteral administration of antiemetics, it is recommended to be guided primarily by the preference and situation of the patient, within the possibilities of the care setting (see paragraph effect of erythromycin).

If anxiety and/or stress also play a role, all the above mentioned agents may be combined with oxazepam 10 mg orally 3 times daily or lorazepam 1-2 mg three times orally, i.v. or possibly sublingually.

Effectiveness of antiemetics on the basis of cause.

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question

What is the effectiveness of the administration of antiemetics chosen on the basis of the cause in patients with nausea and/or vomiting as a result of cancer, heart failure, ALS, MS, COPD or renal failure in the palliative phase?

Recommendation

For patients in the palliative phase with nausea and vomiting as a result of other causes than chemotherapy, ileus, brain metastases or vestibular causes, it is recommended to choose an empirical approach with metoclopramide or domperidone as first choice.

Literatuurbespreking

Introduction

There are many causes of nausea and/or vomiting in patients in the palliative phase [Ang 2010; Glare 2011; Gupta 2012; Harris 2010; Wood 2007]. Various neurotransmitters may play a role in this (such as dopamine, serotonin, histamine or acetylcholine), possibly in conjunction with the underlying cause.

Antiemetics (such as dopamine-antagonists, serotonin-antagonists, antihistamines and anticholinergic agents) affect specific neurotransmitters. It is the question whether the effectiveness of antiemetics is dependent on the underlying cause and the neurotransmitters involved. In the following text, the prevention and treatment of nausea and vomiting as a result of chemotherapy will not be addressed.

Literature discussion

Literature research yielded two studies that were directly related to the clinical question [Bentley 2001; Stephenson 2006]. There were also a number of reviews that paid attention to this approach [Ang 2010; Glare 2011; Gupta 2012; Harris 2010; Wood 2007].
Bentley performed a prospective audit on 37 patients (40 admittances, three patients were admitted twice) with an advanced stage of cancer with nausea and vomiting, who were admitted to a palliative care unit [Bentley 2001]. On admittance, a standard questionnaire was filled in for each patient, in which information was filled in about the patient, the disease and treatment, the symptoms and possible causes. The causes were subdivided into seven groups (with an associated choice of antiemetic): chemical/metabolic (haloperidol) (n=12), gastroparesis/obstruction of the gastric outlet (metoclopramide or domperidone) (n=14), regurgitation (various agents) (n=4), ileus (various agents) (n=5), central nervous system/radiotherapy (cyclizine) (n=1), movement related (cyclizine) (n=0) and other causes/cause unknown (various agents) (n=4). Fifty-nine potentially reversible causes were identified: medication (30), constipation (11), renal failure (7), infection (3), fear (3), gastritis (3) and high obstruction (2). The patients scored the level of nausea and vomiting daily. Metoclopramide (n=15) and haloperidol (n=11) were the most commonly used antiemetics. Domperidone (n=2), cyclizine (n=3), levomepromazine (n=5), butylscopolamine (n=1) and octreotide (n=1) were also used in the first line. Medication was administered orally in 37% of cases and subcutaneous in 63% of cases (as a bolus or continuous). Nausea disappeared completely in 82% of patients, vomiting in 84%.

Stephenson performed a prospective study of 61 patients with an advanced stage of cancer with nausea and vomiting, who were admitted to a hospice [Stephenson 2006]. The treating physician was asked to assign the cause of the nausea to one of six categories (with associated treatment): chemical, including medication,

metabolic causes and infections (haloperidol, n=20), delayed gastric emptying, including tumour, hepatomegaly, medication, ascites, gastritis (metoclopramide, n=27), visceral/serosal, including ileus, gastric bleeding, enteritis, constipation (cyclizine, n=19), central nervous system, including increased intracranial pressure and leptomeningeal metastases (cyclizine, n=50), vestibular (cyclizine, n=0) and anxiety (benzodiazepines, n=4). If there was insufficient effect with the first antiemetic, levomepromazine and/or dexamethasone were prescribed (independent of the cause). On the last evaluation (after one week), 8% did not use antiemetics, 49% one antiemetic, 33% two antiemetics and 10% three antiemetics. The most common drugs were metoclopramide (n=27), levomepromazine (n=27) and dexamethasone (n=17). Other drugs used were haloperidol (n=5), cyclizine (n=4), octreotide (n=4), hyoscine butylbromide (n=2). After 48 hours 44% of the evaluable patients (n=54) did not suffer from nausea and 69% had no vomiting; after 1 week these percentages were 56% and 89% respectively (n=36).

The studies by Bentley and Stephenson show that the approach used for the choice of antiemetic based on cause is reasonably effective in the treatment of nausea and vomiting in patients with an advanced stage of cancer. However, the lack of a control group implies it cannot be concluded that this approach has added value above a structural empirical approach, in which the choice of antiemetic is independent of the cause. This opinion is shared by Ang, Glare and Gupta [Ang 2010; Glare 2011; Gupta 2012]. Harris and Wood propagate the aetiology-based approach [Harris 2010; Wood 2007]. As an argument for this, Wood states that this approach facilitates a systematic approach, takes all possible causes into account and minimises the chance of overtreatment.

Conclusies

It has not been proven that choosing an antiemetic based on the cause of the nausea and/or vomiting has added value above an empirical approach in which the choice of drug is independent of the cause.
Bentley 2001; Stephenson 2006

Overwegingen

While not founded on comparative research, it is rational to choose a prokinetic agent such as metoclopramide or domperidone for nausea and vomiting resulting from a gastroparesis (see also clinical question 11). If an empirical approach is taken it is also rational to choose metoclopramide or domperidone as first choice because these drugs have a broad spectrum of action: they advance gastric emptying (peripheral action) and in addition also have a central antidopaminergic effect.

The treatment of nausea and vomiting due to an ileus or due to brain metastasis, and the prevention and treatment of nausea and vomiting as a result of chemo- or radiotherapy require a different approach. If the cause is vestibular, a scopolamine patch is the agent of first choice; however, this cause is extremely rare in patients in the palliative phase.

Although there is a lack of information about the effect of antiemetics for nausea and vomiting in patients with other diseases than cancer, the recommendation makes no distinction between cancer patients and patients with other life-threatening disorders.

Effect of metoclopramide and domperidone

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2a:

What is the effect of metoclopramide and domperidone in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure and is there a difference in effectiveness between metoclopramide and domperidone?

Recommendation

Metoclopramide is recommended as first chance antiemetic in the treatment of nausea and vomiting in patients in the palliative phase, unless caused by chemotherapy, ileus, brain metastases or vestibular causes. In case of (a high risk of) central side effects that bother the patient, treatment with domperidone is preferred.

Literatuurbespreking

Introduction

Metoclopramide promotes gastric emptying by increasiing peristalsis of the proximal section of the gastrointestinal tract, increasing the tone of the bottom sphincter muscle of the oesophagus and relaxing the pylorus. The antiemetic effect is also the result of antagonism of D2 receptors in the chemoreceptor trigger zone and in the vomiting centre and of antagonism of 5-HT3 receptors. The drug is administered orally (as tablet or drink), rectally or parenterally.

Domperidone is a dopamine antagonist that increases peristalsis of the stomach and duodenum, increases the pressure of the gastro-oesophageal sphincter and also relaxes the sphincter of the pylorus. It also affects the dopamine receptors in the chemoreceptor trigger zone. In contrast to metoclopramide, the drug barely passes the blood-brain barrier., As a result, there are no central side effects (drowsiness, akathisia, dystonia). The drug is administered as tablet, suspension or suppository.
Both drugs are registered for the treatment of nausea and vomiting, independent of the cause.

In the following text, the role of metoclopramide and domperidone in the prevention and treatment of nausea and vomiting as a result of chemotherapy will not be discussed.

Literature discussion

No studies have been found that compare the effectiveness of metoclopramide and domperidone

One review was found in which the effectiveness of domperidone was described for various causes of nausea and/or vomiting [Reddymasu 2007], showing domperidone to be an effective antiemetic. However, the drug has not been studied in patients in the palliative phase. The fact that domperidone is not officially registered in the United States also plays a role in this.

Four articles have been found in which the effect of metoclopramide on nausea and vomiting has been studied in patients in the palliative phase [Bruera 1996 and 2000; Ljutic 2002; Wilson 2002] as well as three reviews [Benze 2012; Davis 2010; Glare 2008] and a protocol of the Cleveland Clinic [Gupta 2012].

In 1996, Bruera conducted a retrospective study on the effect of metoclopramide on nausea and vomiting in 100 patients with cancer in an advanced stage, who were admitted to a palliative care unit [Bruera 1996]. All patients were offered the same medication schedule if they suffered from nausea; first metoclopramide orally or s.c. six

times daily; if that did not help, dexamethasone 10 mg twice daily was added; step 3 was continuous subcutaneous infusion of metoclopramide 60-120 mg/24 hours per day plus dexamethasone. If nausea persisted, patients were switched to a different antiemetic. The visual analogue scale (VAS) scores for nausea were significantly lower than that of other symptoms (anorexia, pain, dyspnoea, unwell). The conclusion was that this schedule with metoclopramide is effective. Other medication was used for 25 patients, especially for patients with intestinal obstruction (n=17) or patients with extrapyramidal side effects (n=3).

Bruera conducted a double-blind cross-over study in 2000 in patients with a cancer-associated dyspepsia syndrome [Bruera 2000]. All patients used an opioid. They were treated with metoclopramide with delayed release 40 mg twice daily or placebo for a duration of 4 days. On day 5, the treatment group was switched for another 4 days. Adjustments in dose and addition of other antiemetics were accepted. The VAS scores for nausea at the end of the treatment period were lower for metoclopramide than placebo (12 vs 17); the VAS scores for vomiting showed a trend for a difference (9 vs 14). There were no differences in side effects.

In 2002, Wilson published a multicentre study on the effectiveness of metoclopramide with controlled release in patients with a cancer-associated dyspepsia syndrome [Wilson 2002]. Forty-eight patients with nausea and vomiting received metoclopramide with controlled release 20-80 mg twice daily for a duration of at least two weeks in an open label group. There was a 40-60% reduction in nausea complaints after two weeks of treatment. There was a 50% reduction in vomiting after 4 weeks.
In a double-blind crossover study [Ljutic 2002], Ljutic compared a single dose of metoclopramide (10 mg i.v.) with ondansetron (8 mg i.v.) in 10 patients with complaints of nausea and vomiting with terminal renal failure. The effect of vomiting was scored on a scale of 1-3 by both the patient and the researcher. Nausea was scored by the patients on a scale of 1-5. High scores indicated a better effect. Ondansetron was more effective than metoclopramide against nausea (average score 4.10 vs 2.10) and vomiting (average score 2.80 vs 1.40).

Reviews state that the evidence for effectiveness of all antiemetics researched (including metoclopramide and domperidone) is of moderate quality [Benze 2012; Davis 2010; Glare 2008]. Benze and Davis recommended using metoclopramide as first line treatment. According to Glare, metoclopramide has the advantage that it can be administered parenterally and domperidone has the advantage that it does not show side effects due to the inability to pass the blood-brain barrier [Glare 2008 34]. He advises against the use of metoclopramide if there is an ileus. In the Cleveland protocol, metoclopramide is the treatment of first choice (except if there is an ileus or brain metastasis) [Gupta 2012].

Conclusies

There are indications that metoclopramide is an effective antiemetic in patients with an advanced stage of cancer. [Bruera 1996 and 2000; Wilson 2002]

There are indications that metoclopramide is a less effective antiemetic than ondansetron in patients with terminal renal failure.[Ljutic 2002]

No statement can be made about the effectiveness of metoclopramide in patients with other diseases than cancer and terminal renal failure.

No statement can be made about the effectiveness of domperidone in patients in the palliative phase.

No statement can be made about the difference in effectiveness between metoclopramide and domperidone.

Overwegingen

Despite the lack of evidence, domperidone is used regularly in daily practice for the treatment of nausea and vomiting in patients in the palliative phase. (A high risk of) side effects such as akathisia and drowsiness with

metoclopramide may result in a preference for domperidone [Glare 2008; Bruera 1996]. On the other hand, the use of more than 30 mg daily domperidone is associated with an increased risk of acute cardiac death due to prolongation of the QT-time [Van Roeden 2013]. However, the risk of acute cardiac death is probably very low [Otten 2013].

Metoclopramide can also be administered parenterally, which can be a benefit in some situations.
Metoclopramide has not been studied in patients with other diseases than cancer and terminal renal failure. However, there is no reason to assume that it would be less effective in other diseases in the palliative phase.

Haloperidol

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2b:

What is the effect of haloperidol in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

Haloperidol is recommended for the treatment of nausea and vomiting in the palliative phase as an alternative for metoclopramide or domperidone, especially if there is another indication for this agent (such as hallucinations or (starting) delirium).

Literatuurbespreking

Introduction

Haloperidol is a butyrophenone derivate with a antipsychotic and a small sedating effect. It blocks both dopaminergic (D2) and alpha1-adrenergic receptors and presumably also the dopamine receptors in the chemoreceptor trigger zone. It has a strong central antidopaminergic and a weak central anticholinergic action.

Haloperidol is registered in the Netherlands as medication for nausea and vomiting (excluding vomiting due to travel sickness), if other agents fail or are contraindicated.

In the follwing text, the role of haloperidol in the prevention and treatment of nausea and vomiting as a result of chemotherapy will not be discussed.

Literature discussion

During the literature search, four systematic reviews [Critchley 2001; Davis 2010; Glare 2004; Perkins 2010], one study [Hardy 2010] and a protocol of the Cleveland Clinic [Gupta 2012] were found.
Critchley conducted a systematic review of the antiemetic effect of haloperidol, droperidol or butyrophenone in patients with an advanced stage of cancer [Critchley 2001]. Patients undergoing chemotherapy were excluded. Critchley found four case studies and two case reports. Critchley concluded that, based on this literature, a statement could not be made on the effect of haloperidol for nausea and vomiting in patients with an advanced stage of cancer [Critchley 2001].

Glare conducted a systematic review of the effect of antiemetics in patients with an advanced stage of cancer [Glare 2004]. Two systematic reviews, seven randomised controlled trials and twelve studies or case series were found. Glare concluded that haloperidol may be effective in the treatment of nausea with advanced cancer [Glare 2004].

Perkins conducted a systematic review of the antiemetic effect of haloperidol in the palliative care of patients with nausea and vomiting [Perkins 2010]. No randomised controlled trials or other articles were found that provided information on the effectiveness of haloperidol for nausea or vomiting in the palliative phase. Perkins concluded that there are no randomised studies that provide information on haloperidol as antiemetic in the palliative phase [Perkins 2010].

Davis conducted a systematic review of antiemetics in patients with an advances stage of cancer [Davis 2010]. He also did not find evidence for the effectiveness of haloperidol.

Hardy conducted a clinical study that included 42 patients with cancer who suffered from nausea and/or vomiting that was unrelated to chemotherapy [Hardy 2010]. Nausea and/or vomiting were both measured using a 0-4 point scale. Patients were treated with haloperidol at two dosage levels: 1) 1.5 orally once daily or 1.5 mg s.c./24 hours, or 2) 1.5 mg orally twice daily or 3 mg/24 hours. Patients were treated for five days. On day two, 33 patients were evaluable for response, on day 5 twenty-three patients. Responses on day two and five were seen in 61% and 74%, respectively, of all evaluable patients. If the non-evaluable patients were included, the response percentages were 47% and 40%, respectively. The researchers concluded that haloperidol has some effectiveness in the treatment of nausea and vomiting.

Gupta wrote "The Cleveland Clinic Protocol" for the treatment of patients with nausea and vomiting in the 'Harry R Horvitz Center for Palliative Medicine' [Gupta 2012]. Gupta concluded that on the basis of practice-based medicine within the palliative expertise centre of the Cleveland Clinic, it is recommended to use haloperidol (1 mg orally twice daily or 5 mg/24 hours s.c. or i.v.) as second choice after metoclopramide.

Conclusies

There are indications that haloperidol is an effective antiemetic in patients with an advanced stage of cancer. Hardy 2010

Overwegingen

In daily practice, haloperidol is used often and with good effect in the treatment of nausea and vomiting. Haloperidol has a more limited mode of action compared to metoclopramide and domperidone because it is only a dopamine-antagonist and not a prokinetic agent. It is not rational to use haloperidol in patients who do not respond sufficiently to metoclopramide or domperidone in adequate doses.

Haloperidol can be used for multiple symptoms in the terminal phase at the same time, such as confusion, which is common in the last week before death [Klinkenberg 2004].

Dexamethasone

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2c:

What is the effect of dexamethasone in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

The guideline development group is of the opinion that dexamethasone monotherapy may be used in the treatment of nausea and vomiting in the palliative phase if there is insufficient response to treatment with metoclopramide, domperidone or haloperidol.

Literatuurbespreking

Introduction

Dexamethasone is a corticosteroid. The agent has a broad area of application due to its anti-inflammatory action. The method of action with nausea and vomiting is not known.

It may be administered orally, subcutaneously or intravenously. The agent is registered for the symptomatic treatment of brain metastases and for the prevention and treatment of nausea and vomiting as a result of chemotherapy.

In the following text, the role of dexamethasone with brain metastases in the prevention and treatment of nausea and vomiting as a result of chemotherapy will not be discussed.

Literature discussion

During the literature research, one randomised study was found in which dexamethasone was compared to placebo, as a supplement to the use of metoclopramide [Bruera 2004]. In this study, 51 patients with an advanced stage of cancer were included who reported persistent complaints of nausea despite having used metoclopramide for 48 hours. Aside from 40-60 mg metoclopramide per day, 25 patients received additionally dexamethasone 10 mg twice daily per day, 26 patients received a placebo. After 8 days, there was a significant reduction in nausea in both groups. There was no significant difference in nausea between the two groups. It was concluded that dexamethasone does not provide additional value when using metoclopramide. The researchers indicated in the discussion that the period of 48 hours of treatment with metoclopramide was maybe too short to evaluate its effect and that the improvement in nausea in patients using a placebo could be a late effect of the treatment with metoclopramide.

Mystakidou conducted a randomised study in 280 patients in an advanced stage of cancer with nausea and vomiting, who did not respond to treatment with metoclopramide [Mystakidou 1998a]. The patients were randomised between treatment for a duration of 14 days with 1) metoclopramide 10 mg four times daily + dexamethasone 2 mg once daily (n=40), 2) tropisetron 5 mg once daily (n=40), 3) metoclopramide 10 mg twice daily + tropisetron 5 mg once daily (n=40), 4) metoclopramide 10 mg twice daily + tropisetron 5 mg once daily + dexamethasone 2 mg once daily (n=40), 5) chlorpromazine 25 mg twice daily + dexamethasone 2 mg once daily (n=40), 6) chlorpromazine 25 mg twice daily + tropisetron 5 mg once daily (n=40), and 7) chlorpromazine 2dd 25 mg twice daily + tropisetron 5 mg once daily + dexamethasone 2 mg once daily (n=40) [Mystakidou 1998a]. In a second publication, the results of groups 2, 5, 6 and 7 were outlined further [Mystakidou 1998b]. The patients completed a diary, in which they recorded how many hours per day they suffered from nausea and how often they

vomited. In all groups treated with tropisetron, a maximum effect on both nausea and vomiting was achieved after 3 days of treatment. Complete control of the nausea after 3 days was seen in 10% of cases (metoclopramide + dexamethasone), 30% (tropisetron), 35% (metoclopramide + tropisetron), 55% (metoclopramide + tropisetron + dexamethasone), 10% (chlorpromazine + dexamethasone), 42% (chlorpromazine + tropisetron) and 60% (chlorpromazine + tropisetron + dexamethasone), respectively. Complete control of vomiting after 3 days was seen in 9% of cases (metoclopramide + dexamethasone), 42% (tropisetron), 65% (metoclopramide + tropisetron), 75% (metoclopramide + tropisetron + dexamethasone), 8% (chlorpromazine + dexamethasone), 67% (chlorpromazine + tropisetron) and 77% (chlorpromazine + tropisetron + dexamethasone), respectively. Comparisons between subgroups suggest that the addition of dexamethasone to the combination of metoclopramide or chlorpromazine and tropisetron leads to a slightly better control of nausea and vomiting. No correction was made for multiple testing.

The results from the study by Mystakidou suggest that tropisetron is effective in the treatment of nausea and vomiting, but the statistical analysis is questionable due to the lack of correction for the large number of comparisons.

Mystakidou also conducted a randomised study in 120 patients in an advanced stage of cancer with nausea and vomiting, who did not respond to treatment with metoclopramide [Mystakidou 1997]. All patients used opioids. They were randomised between metoclopramide10 mg four times daily + dexamethasone 2 mg once daily (n=40), metoclopramide 10 mg twice daily + tropisetron 5 mg once daily (n=40) and metoclopramide 10 mg twice daily + dexamethasone 2 mg once daily + tropisetron 15 mg once daily (n=40). The patients completed a diary, in which they recorded how many hours per day they suffered from nausea and how often they vomited. Complete control of nausea after 14 days was seen in 18%, 74% and 87% of patients, respectively, and complete control of vomiting in 24%, 84% and 92% of patients, respectively. Side effects (weakness, dizziness and constipation occurred in 22 patients.

In a review, no evidence was found for the effect of dexamethasone on nausea and vomiting due to other causes than ileus [Davis 2010]. The effect of dexamethasone monotherapy has not been researched.

In the Cleveland protocol [Gupta 2012], dexamethasone is only recommended if there is nausea and vomiting in patients with an ileus or brain metastases.

Conclusies

There are indications that the addition of dexamethasone does not have an effect in patients with an advanced stage of cancer, who suffer from persistent nausea despite treatment with metoclopramide for a duration of 48 hours.
[Bruera 2005]

No statemade can be made about the effectiveness of dexamethasone monotherapy for nausea and vomiting in patients in the palliative phase.

Overwegingen

The use of dexamethasone in the treatment of nausea and vomiting due to other causes than ileus, brain metastases and chemotherapy is not supported by research. Despite this, the agent is often used successfully in daily practice in treating nausea and vomiting if an insufficient effect is achieved with metoclopramide and/or domperidone. An additional argument for the use of dexamethasone is that it also often has a favourable effect on other complaints that are also common in the palliative phase, such as anorexia, fatigue and pain.

Side effects as a result of long-term use of dexamethasone are less relevant for the patient population concerned.

Levomepromazine

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2d:

What is the effect of levomepromazine in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

Treatment with levomepromazine orally (alternatively buccally or s.c.) is recommended for patients in the palliative phase with nausea and/or vomiting that responds insufficiently to other antiemetics.

Literatuurbespreking

Introduction

Levomepromazine is a phenothiazine derivative with antidopaminergic, antiserotonergic, anticholinergic and antihistaminic action [Dietz 2013]. It may be administered orally, subcutaneously or intravenously. Sedation is the most important side effect.
It is not registered in the Netherlands for the treatment of nausea and vomiting.

In the following text, the role of levomepromazine in the prevention and treatment of nausea and vomiting as a result of chemotherapy will not be discussed.

Literature discussion

Two uncontrolled studies [Eisenchlas 2005; Kennet 2004] as well as two systematic reviews [Davis 2010; Dietz 2013] were found during the literature research.

Eisenchlas described a prospective open-label study in 70 patients with an advanced stage of cancer who suffered from severe nausea and/or vomiting (numeric rating scale (NRS) >7 on a scale of 0-10). All patients were treated previously with other antiemetics (especially metoclopramide, haloperidol and dexamethasone). The median dose of levomepromazine was 6.25 mg once daily (range 3-25) as subcutaneous bolus. After 48 hours, the NRS for nausea decreased by >6 points for 86% of patients; in 92% of patients who were vomiting, the vomiting disappeared completely. For all twelve patients who had a gastric tube due to the vomiting, the gastric tube could be removed. The median sedation score was 2; nine patients (13%) had a sedation score >3 [Eisenchlas 2005].

Kennet conducted a prospective open-label study in 65 patients (of which 53 were evaluable after 2 days and 34 after 5 days) with an advanced stage of cancer with a score for nausea or vomiting of >1 on a scale of 0-3. 57/65 patients were treated earlier with one or more antiemetics (mostly metoclopramide and cyclizine). Most patients received 12.5 mg orally once daily or 6.25 mg/24 hours as continuous subcutaneous infusion. After two and five days, 26% and 35% of patients had a complete remission (complete disappearance of nausea and/or vomiting), respectively, and 36% and 23% a partial remission (reduction of scores of nausea and/or vomiting)[Kennet 2004].

Both reviews concluded that, based on non-comparative prospective research, levomepromazine can be considered an effective antiemetic [Davis 2010; Dietz 2013].

Conclusies

There are indications that levomepromazine is an effective antiemetic for patients with an advanced stage of cancer, who have responded insufficiently to previous antiemetics. [Eisenchlas 2005; Kennet 2004]

Overwegingen

Levomepromazine has not been studied in patients with diseases other than cancer. However, there is no reason to assume that it would be less effective in other diseases. For patients with therapy-resistant nausea and/or vomiting and a disease other than cancer, treatment with levomepromazine may therefore also be considered. While a large proportion of patients in the research studies by Eisenchlas and Kennet were treated with subcutaneous levomepromazine, oral administration is preferable. It is recommended to administer the lowest possible effective dose, due to drowsiness as a possible side effect.

Levomepromazine is not reimbursed. However, given the low costs, this is not a reason not to prescribe the drug.

Olanzapine

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2e:

What is the effect of olanzapine in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

Treatment with olanzapine orally is recommended for patients in the palliative phase with nausea and/or vomiting that responds insufficiently to other antiemetics.

Literatuurbespreking

Introduction

Olanzapine is an antipsychotic agent with antidopaminergic, antiadrenergic, antiserotonergic, anticholinergic and antihistaminic action [Licup 2010]. It is administered in oral (as tablet, also orodispersable) or intramuscular form (for delayed release).
It is not registered in the Netherlands for the treatment of nausea and vomiting.

In the following text, the role of olanzapine in the prevention and treatment of nausea and vomiting as a result of chemotherapy or an ileus will not be discussed.

Literature discussion

During the literature research, a pilot study [Passik 2002], two case series [Jackson 2003; Srivastava 2003] and a systematic review [Davis 2010] were found.
Passik researched 15 patients with an advanced stage of cancer with nausea (NRS score 4-8 on a scale of 0-10) and stable pain, treated with opioids [Passik 2002]. Data on earlier treatment with antiemetics was not reported. Patients did not use other antiemetics during the study. Olanzapine was administered (after two days of treatment with placebo) in successive doses of 2.5, 5 and 10 mg orally once daily, each dose for a duration of 2 days. A significant reduction in nausea was seen at all dose levels. No extrapyramidal side effects or cognitive function disorders occurred.

Jackson described six patients (four with cancer, one with CVA and one with dementia) with therapy-resistant nausea [Jackson 2003]. After treatment with olanzapine 2.5-5 mg orally in the evenings, there was a strong improvement in nausea complaints.
Srivastava described two patients with an advanced stage of cancer and nausea and vomiting, resistant against other antiemetics [Srivastava 2003]. After treatment with olanzapine 5 mg once daily, there was a marked improvement in the nausea and vomiting. Sedation was the most common side effect.

The systematic review concluded that olanzapine is an effective antiemetic on the basis of prospective uncontrolled research [Davis 2010].

Conclusies

There are indications that olanzapine is an effective antiemetic for patients with an advanced stage of cancer, who

have responded insufficiently to earlier antiemetics.
[Jackson 2003; Passik 2002; Srivastava 2003]

Overwegingen

Olanzapine has only been studied in a few patients with diseases other than cancer. However, there is no reason to assume that it would be less effective in other diseases. For the (rare) patient with therapy-resistant nausea and/or vomiting and a disease other than cancer, treatment with olanzapine may therefore also be considered. It is recommended to administer the lowest possible effective dose, due to possible drowsiness as side effect.

In clinical practice, olanzapine is less commonly used than levomepromazine.

Serotonine-antagonists

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2f:

What is the effect of serotonin antagonists in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

Treatment with serotonin antagonists is recommended for patients in the palliative phase:

- to prevent or treat nausea and vomiting as a result of chemotherapy, radiotherapy or postoperatively
- for nausea and/or vomiting that does not respond sufficiently to earlier treatment with metoclopramide, domperidone, haloperidol, dexamethasone and levomepromazine
- as first line treatment in patients with terminal renal failure with nausea and vomiting

Literatuurbespreking

Introduction

Serotonin (5HT3) antagonists, such as ondansetron, granisetron, tropisetron and palonosetron are the antiemetic of choice with moderately and strongly emetogenic chemotherapy, with nausea and vomiting after radiotherapy and with postoperative nausea and vomiting.
They are also applied in the case of nausea and vomiting due to other causes than chemotherapy, radiotherapy or surgery. However, they are not registered for this indication.

In the following text, the role of serotonin antagonists in the prevention and treatment of nausea and vomiting as a result of chemotherapy will not be discussed.

Literature discussion

During the literature research, a systematic review [Davis 2010], four randomised studies [Hardy 2002; Ljutic 2002; Mystakidou 1997; 1998a and 1998b], two retrospective studies [Currow 1997; Weschules 2006], a case series [Porcel 1998] and five case reports [Buchanan 2007; Cole 1998; Macleod 2000; Mercadante 1998; Pereira 1996] were found. Nine studies concerned ondansetron [Cole 1998; Currow 1997; Hardy 2002; Ljutic 2002; Macleod 2000; Mercadante 1998; Pereira 1996; Porcel 1998; Weschules 2006], two concerned tropisetron [Mystakidou 1997; 1998a and 1998b] and two concerned granisetron [Buchanan 2007; Porcel 1998]. Most studies were performed in patients with an advanced stage of cancer.

Mystakidou conducted a randomised study in 280 patients in an advanced stage of cancer with nausea and vomiting, who did not respond to treatment with metoclopramide [Mystakidou 1998a]. The patients were randomised between treatment for a duration of 14 days with 1) metoclopramide 10 mg four times daily + dexamethasone 2 mg once daily (n=40), 2) tropisetron 5 mg once daily (n=40), 3) metoclopramide 10 mg twice daily + tropisetron 5 mg once daily (n=40), 4) metoclopramide 10 mg twice daily + tropisetron 5 mg once daily + dexamethasone 2 mg once daily (n=40), 5) chlorpromazine 25 mg twice daily + dexamethasone 2 mg once daily (n=40), 6) chlorpromazine 25 mg twice daily + tropisetron 5 mg once daily (n=40), and 7) chlorpromazine 2dd 25 mg twice daily + tropisetron 5 mg once daily + dexamethasone 2 mg once daily (n=40) [Mystakidou 1998a]. In a second publication, the results of groups 2, 5, 6 and 7 were outlined further [Mystakidou 1998b]. The patients completed a diary, in which they recorded how many hours per day they suffered from nausea and how often they vomited. In all groups treated with tropisetron, a maximum effect on both nausea and vomiting was achieved after 3 days of treatment. Complete control of the nausea after 3 days was seen in 10% of cases (metoclopramide +

dexamethasone), 30% (tropisetron), 35% (metoclopramide + tropisetron), 55% (metoclopramide + tropisetron + dexamethasone), 10% (chlorpromazine + dexamethasone), 42% (chlorpromazine + tropisetron) and 60% (chlorpromazine + tropisetron + dexamethasone), respectively. Complete control of vomiting after 3 days was seen in 9% of cases (metoclopramide + dexamethasone), 42% (tropisetron), 65% (metoclopramide + tropisetron), 75% (metoclopramide + tropisetron + dexamethasone), 8% (chlorpromazine + dexamethasone), 67% (chlorpromazine + tropisetron) and 77% (chlorpromazine + tropisetron + dexamethasone), respectively. Comparisons between subgroups suggest that the addition of dexamethasone to the combination of metoclopramide or chlorpromazine and tropisetron leads to a slightly better control of nausea and vomiting. No correction was made for multiple testing.

The results from the study by Mystakidou suggest that tropisetron is effective in the treatment of nausea and vomiting, but the statistical analysis is questionable due to the lack of correction for the large number of comparisons.
Two randomised studies researched the effect of ondansetron with opioid-induced nausea and vomiting in patients with cancer [Hardy 2002; Mystakidou 1997].

In a randomised, double-blind setting, Hardy compared 24 mg ondansetron orally once daily (n=29) with metoclopramide 10 mg three times daily(n=33) and placebo (n=30) in patients with cancer who had nausea and vomiting as a result of opioids [Hardy 2002 41]. The study was ended prematurely due to difficulty with inclusion of patients. No significant differences were seen between the groups in relation to complete control of nausea and vomiting after 24 hours of treatment. However, the power of the study to show a difference was limited due to small patient numbers.

Mystakidou conducted a randomised study in 120 patients in an advanced stage of cancer with nausea and vomiting, who did not respond to treatment with metoclopramide [Mystakidou 1997]. All patients used opioids. They were randomised between metoclopramide10 mg four times daily + dexamethasone 2 mg once daily (n=40), metoclopramide 10 mg twice daily + tropisetron 5 mg once daily (n=40) and metoclopramide 10 mg twice daily + dexamethasone 2 mg once daily + tropisetron 15 mg once daily (n=40). The patients completed a diary, in which they recorded how many hours per day they suffered from nausea and how often they vomited. Complete control of nausea after 14 days was seen in 18%, 74% and 87% of patients, respectively, and complete control of vomiting in 24%, 84% and 92% of patients, respectively. Side effects (weakness, dizziness and constipation occurred in 22 patients.

In a double-blind crossover study [Ljutic 2002], Ljutic compared a single dose of metoclopramide (10 mg i.v.) with ondansetron (8 mg i.v.) in 10 patients with complaints of nausea and vomiting with terminal renal failure. The effect of vomiting was scored on a scale of 1-3 by both the patient and the researcher. Nausea was scored by the patients on a scale of 1-5. High scores indicated a better effect. Ondansetron helped more than metoclopramide against nausea (average score 4.10 versus 2.10) and vomiting (average score 2.80 versus 1.40).

Weschules conducted a retrospective cohort study in patients in a home care programme in which the results of collaborative practice protocols for pain, sleeplessness and nausea and vomited were compared retrospectively with the results of treatment with new drugs [Weschules 2006]. Treatment with prochlorperazine (n=45) was compared with ondansetron (n=45) in relation to nausea and vomiting. All patients were in the palliative phase; patients who were treated with ondansetron more often had cancer than patients who were treated with prochlorperazine (44 versus 27). The number of complete responses (total disappearance of nausea and vomiting) after 1-2 weeks was higher in the prochlorperazine group (49% versus 27%).

In a retrospective study, Currow described the effect of treatment with ondansetron in a dose of 8-24 mg per day, divided over 2-3 doses with 16 patients (seven with cancer and nine with AIDS), who were admitted to a hospice [Currow 1997]. All patients were treated earlier with other antiemetics. The response after 48 hours was evaluated on the basis of scores for nausea and vomiting by the health care providers. Nausea improved in 12 out of 15 and vomiting in 10 out of 14 patients.

Porcel described the effect of ondansetron 8 mg s.c. three times daily (n=6) or 3 mg granisetron s.c. once daily (n=4) in patients with an advanced stage of cancer with nausea and vomiting, who had responded insufficiently to treatment with other antiemetics [Porcel 1998]. Nine patients experienced a clear and rapid improvement in

vomiting.

Different case reports described favourable effects for granisetron s.c. in two patients with metastatic breast cancer and a metastatic ovarian carcinoma respectively with therapy-resistant nausea and vomiting [Buchanan 2007] and for ondansetron in patients with cancer [Cole 1998; Mercadante 1998; Pereira 1996] and with two patients with multiple sclerosis [Macleod 2000]. The systematic review concluded that ondansetron is an effective antiemetic (based on cohort studies, retrospective studies, case series or case reports) [Davis 2010]. No conclusion was drawn about other serotonin antagonists.

Conclusies

There are indications that ondansetron, granisetron and tropisetron are effective antiemetics for nausea and vomiting in patients with an advanced stage of cancer, AIDS or multiple sclerosis, who have responded insufficiently to earlier antiemetics.
[Buchanan 2007; Cole 1998; Currow 1997; Macleod 2000; Mystakidou 1998-1 and 1998-2; Porcel 1998]

No statement can be made about the effectiveness of serotonin antagonists for nausea and vomiting as a result of opioids due to poor quality of research and conflicting results.
[Hardy 2002; Mystakidou 1997]

There are indications that ondansetron is more effective than metoclopramide for nausea and vomiting in patients with terminal renal failure.
[Ljutic 2002]

Overwegingen

Given research and experience in patients experiencing nausea and vomiting due to chemotherapy [Bilio 2010], there is no reason to assume that there are differences in effectiveness or side effects between ondansetron, granisetron or tropisetron. No statement can be made as to which drug is preferable.

The side effects of serotonin antagonists have not been systematically researched and reported in the studies discussed. Experience in patients being treated with serotonin antagonists who suffer from nausea and vomiting due to chemotherapy shows that constipation is a common problem.

The costs of oral administration of serotonin antagonists amount to €10-14 per day (compared to metoclopramide €0.20-0.35 per day and domperidone €0.30-0.60 per day).

Cyclizine

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2g:

What is the effect of cyclizine in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

Due to a lack of research and clinical experience, no recommendations can be made about the use of cyclizine in the treatment of nausea and vomiting in patients in the palliative phase.

Literatuurbespreking

Introduction

Cyclizine is an antihistamine drug with weak anticholinergic and strong anti-emetogenic properties. The drug is frequently used in England. In the Netherlands, it is registered for travel sickness and for nausea and vomiting as a result of various causes, including opioid use and radiotherapy.

Literature discussion

No literature has been found on the effect of cyclizine on nausea and vomiting in patients in the palliative phase.

Conclusies

No statement can be made about the effectiveness of cyclizine for nausea and vomiting in patients in the palliative phase.

Overwegingen

Cyclizine is not commonly used in the Netherlands for patients in the palliative phase. Members of the guideline development group do not have experience with the drug.

Erytromycine

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2h:

What is the effect of erythromycin in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

Erythromycin is not recommended for the treatment of nausea or vomiting for patients in the palliative phase, unless there is gastroparesis due to diabetes mellitus or after vagotomy.

Literatuurbespreking

Introduction

Erythromycin is a motilin agonist and therefore has a prokinetic action. It induces antral contractions with acceleration in gastric emptying [Annesse 1992]. This has been demonstrated in healthy volunteers but also in patients with gastroparesis as a result of diabetes mellitus [Tack 1992; Kendall 1997] or after a vagotomy [Kendall 1997].

As prokinetic agent, erythromycin is usually administered intravenously. It can also be administered orally. If used for more than a few weeks, tachyphylaxia develops due to downregulation of the motilin receptor. The clinical response decreases after 4 weeks use of oral erythromycin [Richards 1993].

Erythromycin is affected by interactions with drugs metabolised by CYP3A4. Administration of erythromycin is also associated with the development of corrected QT interval prolongation.

Literature discussion

There were 375 publications found during literature research, of which 200 were after 1998. The great majority concerns the use of erythromycin in patients with gastroparesis, especially as a result of diabetes mellitus. In the studies involving gastroparesis, none looked specifically at malignancy-associated gastroparesis.
There is one study involving patients with postoperative gastroparesis [Ramirez 1994]. There are also 2 retrospective case series that report the use of erythromycin after radiotherapy or bone marrow transplantation without quantifying the effect [Brand 1998; Eagle 2001].

No studies have been found that involve treatment of nausea and/or vomiting that is not related to demonstrated gastroparesis.

While erythromycin has a stronger effect on gastric emptying than domperidone and metoclopramide, this does not always correlate with an improvement in symptoms [Sturm 1999].

Erythromycin is effective for diabetic gastroparesis and after vagotomy. If one of these two disorders is the cause of the nausea or vomiting, erythromycin may be considered. After approximately 4 weeks, there is a risk of tachyphylaxis with the resulting possible reduction in efficacy.

Conclusies

No statement can be made about the effect of erythromycin in patients in the palliative phase with nausea and vomiting.

Medicinal cannabis

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2i:

What is the effect of medicinal cannabis in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

Medicinal cannabis is not recommended for patients in the palliative phase of nausea and/or vomiting.

Literatuurbespreking

Introduction

Medicinal cannabis (dronabinol (THC), cannabidiol (CBD) binds to cannabinoid receptors in the central and peripheral nervous system. The agonistic effect of cannabinoid agents on these receptors in the central nervous system inhibits neurotransmission, so that the central mechanism of nausea is inhibited.

Medicinal cannabis is administered orally (liquid; tea) or inhaled by means of a nebuliser. Medicinal cannabis is registered in the Netherlands for the treatment of nausea and vomiting. Medicinal cannabis products that are currently available on the market in the Netherlands are: Bedrocan, Bedrobinol and Bediol (granulate).

There are indications that medicinal cannabis has an effect on nausea and vomiting with chemotherapy [Machado 2008; Tramer 2001]. This will not be discussed further here.

Literature discussion

No literature has been found on the effect of medicinal cannabis in patients in the palliative phase with nausea and vomiting.

Conclusies

No statement can be made about the effectiveness of medicinal cannabis for nausea and/or vomiting in patients in the palliative phase.

Overwegingen

The use of medicinal cannabis may be associated with central side effects, like dizziness (48%), dysphoria/depression (12%), hallucinations (6%) and paranoid delusions (5%) [Tramer 2001].

Ginger

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 2j:

What is the effect of ginger in the treatment of nausea and/or vomiting in patients in the palliative phase of cancer, heart failure, COPD, MS, ALS or renal failure?

Recommendation

Ginger is not recommended for patients in the palliative phase with nausea and/or vomiting.

Literatuurbespreking

Introduction

Ginger (zingiberis rhizoma) is an herb used in complementary medicine to treat nausea. There are indications that ginger has an effect on nausea resulting from chemotherapy as well as nausea during pregnancy. The mechanism of action is not known. It is possible that the mechanism involves interaction with 5HT3 receptors via the component galanolactone [Lumb 1993].
Ginger is administered orally. Ginger is not registered in the Netherlands as a medicine.

Literature discussion

One review [Quimby 2007] was found during literature research.
Quimby performed a review on the use of ginger by cancer patients. He outlines the results of an earlier review on the use of ginger for nausea and vomiting [Ernst 2000} and the results of three studies on the use of ginger for nausea due to chemotherapy [Sharma 1997 and 1998; Zick 2005]. No outcome measures are provided. Quimby concludes that ginger reduces complaints of nausea for both nausea during pregnancy and nausea after chemotherapy [Quimby 2007]. No statement is made about nausea and/or vomiting in the palliative phase.

Conclusies

No statement can be made about the effectiveness of ginger for nausea and/or vomiting in patients in the palliative phase.

Overwegingen

There are no reports of side effects of ginger.

Parenteral and rectal administration of antiemetics

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Aanbevelingen

Clinical question 3:

What are the differences in effectiveness between parenteral and rectal administration of antiemetics in patients with nausea and/or vomiting as a result of cancer, heart failure, COPD, ALS, MS or renal failure in the palliative phase?

Recommendation

When making a choice between rectal or parenteral administration of antiemetics, it is recommended to be primarily guided by the preference and situation of the patient, however within the possibilities of the care setting.

Literatuurbespreking

Introduction

In general, oral administration of antiemetics is preferable. When oral administration is not possible or desirable, a choice can be made for rectal or parenteral administration.

Literature discussion

One article has been found in which a comparison is made between rectal and intravenous administration of metoclopramide [Hardy 1990]. The article studied the pharmacokinetics of a dose of 150 mg metoclopramide, administered as a suppository (n=6) or as an intravenous bolus (dissolved in 10 ml 0.9% NaCl, administered in 10 minutes, n=5) to patients who were being treated with chemotherapy. Three patients received metoclopramide rectally as well as i.v. with a 48-hour time interval. Plasma levels were measured over 24 hours. Both forms of administration gave effective plasma levels. For the three patients receiving metoclopramide both intravenously and via a suppository, the suppository provided total systemic availability of metoclopramide.

The article does not make a pronouncement about the differences in burden on the patient. No literature was found on the burden on the patient.

Conclusies

There are indications that rectal and intravenous administration of metoclopramide yield comparable plasma levels.
[Hardy 1990].

No statement can be made about differences in burden associated with the form in which antiemetics is administered.

Overwegingen

Whether rectal administration or parenteral administration of antiemetics is the least burdensome on the patient, is dependent on the preference and situation of the patient. In addition, it depends on the care setting whether

parenteral administration is possible. Parenteral administration requires extra materials and competent staff. There is also a difference in costs: parenteral administration is much more expensive than rectal administration.

Stepwise approach

Vastgesteld: 16-06-2014 Regiehouder: IKNL

Diagnostics

1. Patient history and physical examination
2. Laboratory analysis to assess dehydration and/or potassium loss: serum urea, serum creatinine, serum potassium
3. If a specific cause is suspected: laboratory analysis (Na, Ca^{2+}, glucose), X-BOZ, abdominal ultrasound/CT scan, image of the small intestine with gastrografphn, gastroscopy, brain CT/MRI

Management plan

1. If possible: treat the cause:
    - targeted antitumour therapy
    - modification of the dose or discontinuation of medication
    - stent or gastrojejunostomy in the case of obstruction of the pylorus or duodenum
    - treatment of pain, constipation, cough, reflux, peptic ulcer, gastritis, gastroenteritis, pancreatitis, cholelithiasis, nephrolithiasis or cystitis
    - treatment of hypercalcaemia or hyponatraemia
    - with ascites: ascites puncture or possibly diuretics
    - surgery, stent or chemotherapy in the case of ileus
    - radiotherapy or resection of brain metastases
2. Symptomatic management:
    - non-pharmacological symptomatic treatment:
        - if required: parenteral administration of fluid and potassium
        - nutritional and lifestyle advice
        - for severe vomiting caused by pyloric obstruction or obstruction of the duodenum, ileus or gastroparesis: temporary or permanent gastric draining using a nasogastric or PEG tube
        - consider acupuncture and/or acupressure, complementary forms of care and/or psychological techniques
    - pharmacological symptomatic treatment
        - with gastroparesis:
            - metoclopramide 10-20 mg orally 3-4 times daily or 3-4 dd 20-40 mg rectally 3-4 times daily or 40-100 mg/24 hrs s.c. or i.v., or
            - domperidone 10-20 mg orally or 60-120 mg rectally 3-4 times daily
        - in the case of ileus:
            - somatostatin analogues: octreotide 100-300 microgram s.c. three times daily or 300 - 900 microgram/24 hours continuous s.c. or i.v. infusion (particularly for severe vomiting); or (during the stable phase after the efficacy of octreotide has been confirmed) ocreotide LAR 30 mg i.m. every 4 weeks or lanreotide PR 30 mg i.m. once every 2 weeks
            - hyoscine butylbromide 40-120 mg/24 hours s.c. or i.v.
        - in the case of patients treated with chemotherapy or radiotherapy:
            - prophylactically with radiotherapy or <24 hours after administration of moderately to highly emetogenic chemotherapy: ondansetron 8 mg orally or i.v. twice daily or 16 mg rectally once daily, granisetron 1 mg orally twice daily or 3 mg i.v. or 3.1 mg/24 hrs transdermal (only if treatment is for multiple days) or tropisetron 5 mg orally once daily or i.v., palonosetron single dose of 250 µg i.v., sometimes in combination with dexamethasone and aprepitant or fosaprepitant
            - if there is nausea and/or vomiting >24 hours after administration of chemotherapy, the following may be chosen: metoclopramide 10-20 mg orally or 20-40 mg rectally 3-4 times daily, domperidone 10-20 mg or 60-120 mg rectally 3-4 times daily, or a dexamethasone in a tapering dose schedule

        - f there is anticipatory nausea or vomiting: 1-2 mg lorazepam orally, s.l. or i.v., prior to chemotherapy
    - if there is nausea or vomiting with terminal renal failure:
        - ondansetron 8 mg orally or i.v. twice daily or 16 mg supp. once daily, granisetron 3 mg i.v. or 1 mg orally twice daily or tropisetron 5 mg orally or i.v. once daily
    - for vestibular causes:
        - scopolamine TTS 1-2 1.5 mg patches every 72 hour

- in all other cases:
    - Step 1
        - metoclopramide 10-20 mg orally or 20-40 mg p.r. 3-4 times daily or 40-120 mg/24 hrs s.c. or i.v., or
        - domperidone 10-20 mg orally or 3-4 dd 60-120 mg rectally 3-4 times daily
    - Arguments for metoclopramide: more experience, based on research in patients in the palliative phase.
    - Arguments for domperidone: presumably just as effective, but less chance of central side effects (extrapyramidal side effects, akathisia = motoric unrest, dystonia, drowsiness)
    - Alternative for metoclopramide or domperidone:
        - haloperidol 1-2 mg orally or 2 dd 0.5 mg s.c. or i.v. twice daily or 1-2 mg/24 hours s.c. or i.v.
    - Step 2
        - dexamethasone (monotherapy) 4-8 mg orally, s.c. or i.v. once daily
    - Step 3
        - levomepromazine (monotherapy): 6.25-12.5 mg orally a.n. or 3.12-6.25 mg s.c. (as monotherapy; non-reimbursable but inexpensive); can also be administered buccally (1 ml=25 mg added to 9 ml tap water; dose of 1 ml of this dilution = 2.5 mg)
    - Alternatives:
        - olanzapine (monotherapy) 5 mg (as monotherapy) once or twice daily
        - serotonin (5HT3) antagonists: ondansetron 8 mg orally twice daily or 1 dd 16 mg p.r., granisetron 1 mg orally twice daily or tropisetron 5 mg orally once daily, in principle in combination with dexamethasone 4 - 8 mg orally once daily. Disadvantages: high costs, constipation as side effect
- If psychological factors also play a role, all the above mentioned agents can be combined with oxazepam 10 mg orally or lorazepam 1-2 mg orally or i.v. three times daily

Levels of evidence

Guideline Nausea and vomiting 3.0

Treatment	Level of incidence	Reference(s)
Opioid rotation or changing the route of administration of opioids	2	Bruera 1995, Drexel 1989, Heiskanen 1997, Kalso 1990, Mercadante 1998
Placement of pyloroduodenal stent	2	Del Piano 2005, Dormann 2004, Hosono 2007, Jeurnink 2007, Johnsson 2004, Mehta 2006, Mittal 2004, Siddiqui 2007
Abdominal paracentesis	3	McNamara 2000
Surgery for bowel obstruction in selected patients	3	Ripamonti 2008

Nasogastric/PEG tube for gastroparesis/obstructed gastric outlet or bowel obstruction		3	Brooksbank 2002, Gemlo 1986, Pothuri 2005
Octreotide for bowel obstruction		2	Mercadante 2000, Mystakidou 2000, Ripamontin 2000
		3	Khoo 1994, Laval 2006, Mangili 1996, Mangili 2005, Shimai 2008
Lanreotide		3	Massacesi 2006, Matoulonis 2005
Butylscopolamine for bowel obstruction		3	Baines 1985, Mercadente 2000, Ripamonti 2000
Nutritional advice		4	LEVV 2007
Acupuncture and acupressure			
	postoperatively	2	Ezzo 2006
	chemotherapy	2	Ezzo 2006, Naeim 2008
	other causes	2	Brown 1992, Nystrom 2008, Perkins 2008, Wright 2005
Complementary therapies and psychological techniques			
	massage	2	Ahles 1999[A], Cassileth 2004, Graelish 2000[A]
	aromatherapy	3	Gilligan 2005
	distraction	3	Vasterling 1993[A]
	progressive muscle relaxation, with(out) guided fantasy excercises	1-2	Luebbert 2001[A], Devine 1995[A]
	listening to music	3	Ezzone 1998[A], Standley 1992[A]
Metoclopramide		2	Bruera 1994, Bruera 1996, Bruera 2000, Shivshankar 1983, Wilson 2002
Domperidone		4	
Erythromycin for gastroparesis		3	Maganti 2003[B]
Haloperidol		4	Critchley 2001, Perkins 2009
Serotonin (5HT3) antagonists for radiotherapy- or chemotherapy-induced nausea and vomiting		1	Herrstedt 2008, Kris 2006, Roila 2006
Serotonin (5HT3) antagonists for nausea and vomiting due to other causes		2	Buchanan 2007, Cole 1998, Currow 1997, Ljutic 2002, Mystakidou 1998, Nicholson 1992, Porcel 1998, Sussman 1999
Dexamethasone for chemotherapy-induced nausea and vomiting (combined with serotonin (5HT3) antagonists)		1	Kris 2006, Naeim 2008

Dexamethasone for nausea and vomiting due to other causes (combined with other antiemetics)	3	Bruera 1996, Hardy 2001, Mystakidou 1998, Bruera 2004
Aprepitant for chemotherapy-induced nausea and vomiting	1	Herrstedt 2008, Kris 2006, Roila 2006
Cyclizine	4	
Scopolamine	4	
Levomepromazine	3	Eisenchlas 2005, Kennett 2005, Skinner 1999, Twycross 1997
Olanzapine	3	Jackson 2003, Passik 2002, Srivastava 2003

[A] Study on nausea and vomiting following chemotherapy

[B] Study in patients with idiopathic or diabetic gastroparesis; no data available on use in patients with cancer in the palliative phase

Level 1 = based on a systematic review or at least two randomised trials of sufficient quality

Level 2 = based on at least two comparative clinical trials of moderate quality or insufficient size, or other comparative studies

Level 3 = based on one comparative trial or a non-comparative trial

Level 4 = based on expert opinion

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