

Yorkshire Palliative Medicine Clinical Guidelines Group

Guidelines on the use of Antiemetics

Author(s): Dr Annette Edwards (Chair) and Deborah Royle on behalf of the Yorkshire Palliative Medicine Clinical Guidelines Group

Overall objective: To provide guidance on the evidence for the use of antiemetics in specialist palliative care.

Search Strategy:

Search strategy: Medline, Embase and Cinahl databases were searched using the words nausea, vomit\$, emesis, antiemetic and drug name.

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Competing interests: None declared

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Contact Details: Dr Annette Edwards, Macmillan Consultant in Palliative Medicine, Department of Palliative Medicine, Pinderfields General Hospital, Aberford Road, Wakefield, WF1 4DG
Tel: 01924 212290
E-mail: annette.edwards@midyorks.nhs.uk

Introduction:

Nausea and vomiting are common symptoms in patients with advanced cancer. A careful history, examination and appropriate investigations may help to infer the pathophysiological mechanism involved. Where possible and clinically appropriate aetiological factors should be corrected. Antiemetics are chosen based on the likely mechanism and the neurotransmitters involved in the emetic pathway. However, a recent systematic review has highlighted that evidence for the management of nausea and vomiting in advanced cancer is sparse. (Glare 2004)

The following drug and non-drug treatments were reviewed to assess the strength of evidence for their use as antiemetics with particular emphasis on their use in the palliative care population.

Cyclizine	Steroids
Haloperidol	Octreotide
Droperidol	Hyoscine
Prochlorperazine	Benzodiazepines
Levomepromazine	Atypical antipsychotics – olanzepine
Metoclopramide	Cannabinoids
Domperidone	NK1 antagonists
Erythromycin	Acupuncture
5HT3 antagonists	Ginger

Guidelines are produced at the end in chart format, suggesting antiemetics for clinical scenarios.

The following drugs are not currently recommended for use and appear in appendix only:

1. Olanzapine - CSM warning about increased risk of stroke in elderly patients with dementia has resulted in decreased use in Yorkshire
2. Droperidol - “black box” warning by FDA in America as prolongs QT interval and is linked to cardiac arrhythmias and risk of cardiac arrest.
3. Erythromycin – insufficient evidence of effectiveness as antiemetic
4. NK1 antagonists – very promising antiemetic for chemotherapy related nausea and vomiting, but currently still only being used in trial setting

NB Other non-pharmacological techniques are sometimes used in the management of nausea and vomiting, including progressive muscle relaxation training, guided imagery, self hypnosis, TENS, biofeedback, cognitive distraction and music therapy. These are not reviewed in these guidelines.

For simplicity the following abbreviations are used:

Post operative nausea and vomiting: PONV

Chemotherapy induced nausea and vomiting: CINV

CYCLIZINE

Pharmacology:

Antihistaminic(H1) anti-muscarinic: Acts on receptors in the vestibular and vomiting centres

NB anticholinergic effect on the bowel

Bioavailability: no data

Onset of action: < 2 hours

Duration of action: 4-6 hours

Plasma half-life: 5 hours

Adverse effects:

Drowsiness

Antimuscarinic effects

Skin irritation with CSCI

NB Detrimental haemodynamic effects in heart failure – increases arterial and ventricular filling pressures, negating venodilatory effects of diamorphine (Tan 1988)

Usual Dose:

Usual maximum daily dose 150mg, PO or CSCI

Evidence:

Palliative Care:

- No trials specific to palliative care

Chemotherapy and radiotherapy related:

- Trials confirm antiemetic effect (Rowlands 76) but use has been superseded by other antiemetics

Post op:

- Placebo-controlled trials confirm effectiveness for nausea post-operatively (Bonica 58, Dundee 66) and after spinal anaesthesia (Nortcliffe 2003)
- Some studies have shown it to be less effective than other antiemetics eg 5HT3 antagonists (Watts 96, O'Brien 2003), or more effective if used in combination with these (Ahmed 2000).

Other clinical situations:

- Evidence of effectiveness for nausea associated with analgesics (Dundee 68,75, Chestnutt 86)

Conclusion:

- Proven anti-emetic
- In certain situations other antiemetics may be more effective eg PONV, CINV.
- Clinical experience favours its use first line in bowel obstruction, raised intracranial pressure and movement induced nausea and vomiting.

HALOPERIDOL

Pharmacology:

Neuroleptic - butyrophenone

Potent dopamine (D2 and ?D1) receptor antagonist – widespread receptors (limbic system, basal ganglia, substantia nigra, brain-stem reticular formation. Also acts on projections from midbrain nuclei to forebrain cortex).

Weak effect on histaminic, muscarinic, alpha adrenoreceptors, opioid and serotonin receptors.

Oral bioavailability 60-70%

Onset of action 10-15 mins sc, >1hr po

Duration of action: up to 24 hours

Variable plasma half-life: 12-38 hours

Steady state within 1 week on steady maintenance dose

Linear relationship between dose and plateau plasma levels

Extensively metabolised in liver (CYP2D6) – 50 – 60% metabolites are inactive

NB Genetic variation in response to drugs e.g. people who are slow oxidisers are at risk of excessive sedation with haloperidol.

Adverse effects:

Extrapyramidal effects (including tardive dyskinesia) - due to dopamine blockage in distal ganglia. Possibly less of a problem with parenteral haloperidol (? ↑ anticholinergic activity antagonizes extrapyramidal effects)

Hypotension (peripheral alpha blocker)

Occasional endocrine effects eg galactorrhea (blocks dopamine mediated prolactin-inhibiting path in hypothalamus)

Weak antimuscarinic and antihistaminic effects including sedation at high doses

Neuroleptic malignant syndrome – see appendix 5

Usual dose range:

Stat dose 0.5 – 5 mg

1.5 – 10 mg / 24 hrs

Evidence

Initial studies in animals confirmed haloperidol's antiemetic effect by acting at D2 receptors.

Palliative Care:

- No specific trials in palliative care – predominantly case reports, case series (describe use in inoperable gastrointestinal obstruction)(Ventifrida 1990) and guidelines.
- Compatibility study with hyoscine-N-butyl bromide in syringe driver - haloperidol precipitates out of solution at concentration >1.25mg/ml with any concentration of buscopan (Barcia 2003)
- Review papers (Tyler 2000, Critchley 2001,) amalgamating data from previous studies suggest its use for nausea and vomiting associated with toxins, infections, cancer metabolites, radiotherapy, drug-induced emesis including epidural morphine and inoperable bowel obstruction

Chemotherapy/ radiotherapy related:

- Trials confirm antiemetic effects, but other more effective agents have superseded its use

- Review concerning anti-emetic usage post radiotherapy (Tonini) suggests D2 antagonists useful for all patients except those receiving total body irradiation (5HT antagonists and corticosteroids preferred)

Post op:

- Several placebo-controlled trials confirm effectiveness, doses usually 0.5 – 4 mg
- Meta-analysis (Buttner 2004) shows NNT to prevent PONV during 24 hours with 0.5 – 4mg haloperidol is 3.2 – 5.1 (no evidence of dose responsiveness)

Other situations:

- Trials have confirmed effectiveness as antiemetic in gastrointestinal disorders (Robbins 1975)
- Meta-analysis (Buttner 2004) for haloperidol in gastroenterology showed 2 mg more effective than 1mg.

Conclusion

- Effective antiemetic
- Cheap
- Compatible with most other drugs in CSCI
- Doses above 5mg/24hrs may not lead to better anti-emetic activity
- Clinical experience suggests first line use for chemical / metabolic causes of nausea in palliative care setting, and as an adjunct in indeterminate causes or bowel obstruction

LEVOMEPRMAZINE

Pharmacology

Phenothiazine antipsychotic.

Broad spectrum of activity: D₂, 5HT₂, alpha 1, H₁ and A Ch muscarinic antagonism

Bioavailability: 40-50%.

Onset of action: 30mins

Duration of action: 12-24 hours

Peak plasma concentration: 30-90 min post im injection, 1-3 hours post oral dose

Plasma half-life: 15-30 hours

Usual dose range:

6-25mg PO od-bd

2.5-25mg SC

Evidence

1. Palliative Care Settings:

- Level of evidence in palliative care patients is poor – predominantly audit related. (Oliver D 1985, Barkby G 1995), or case reports
- Suggest is effective anti-emetic but sedative at 12.5mg or more.
- Fairmile guidelines suggest PRN doses 2.5mg.(Bentley A 2001)

- Link trial still ongoing after modifications.

2. Chemotherapy induced nausea and vomiting:

- Open label study used oral levomepromazine pre-treatment, effective but sedation was limiting factor. (Higi M, 1980)
- Prospective observational study (n =32): evidence for the effectiveness of subcutaneous levomepromazine 25mg / 24hrs in delayed chemotherapy induced emesis (McCabe, 2003). Complete control of nausea in 75% and vomiting in 88% within 24 hours, and 94% of both by 48 hrs.

Conclusion

- Clinical experience suggests is effective broad spectrum anti-emetic, most useful if multiple causes of nausea and vomiting or second line.

PROCHLORPERAZINE

Pharmacology

Piperidine derivative of phenothiazine antipsychotics.

D2 and H1 antagonist

Oral bioavailability 15%

Half life 8hrs for single dose 18 hrs for chronic use

Adverse effects:

Drowsiness

Akathesias - more likely if given iv

Skin irritation with subcut infusions (Trinkle 1997)

Preparations / Usual dose range:

Oral 5-10mg tds

Buccal 3 mg bd (equivalent to 5mg tds orally)

Suppository 5mg tds (25 mg also available)

Evidence

Palliative Care:

- No research evidence specific to palliative care

Chemotherapy related:

- More effective than placebo in mildly emetogenic regimes (Bakowski 1984) now superseded by other agents

Post operative:

- Better than placebo. Buccal preparation has quicker onset of action. (Williams1999, Singh 1999)

Acute nausea and vomiting (eg gastroenteritis, associated with vertigo):

- Effective - studies frequently use parenteral preparation (Ernst 2000, Ordog 1984,)

Conclusion

- Effective antiemetic, but has been superseded by most other antiemetics in many specialist palliative care units.
- Theoretically effective vs D₂-mediated emesis. Buccal preparation has better bioavailability, quicker onset and longer duration of action.
- Buccal and suppository preparations may be particularly useful for use in community.

NB In addition to levomepromazine and prochlorperazine, other phenothiazines are occasionally used as antiemetics eg promethazine and chlorpromazine.

METOCLOPRAMIDE

Pharmacology

Prokinetic
Dopamine antagonist (D₂)
5HT₄ agonist (most important activity)
5HT₃ antagonist (>100mg/24 hrs)

Bio-availability: 50-80% PO
Onset of action: 10-15 min IM; 15-60min PO
Duration of action: 1-2 hrs (data for single doses and relate to gastric emptying)
Plasma half life 2.5-5hrs

Adverse effects

Extrapyramidal
Acute dystonic reactions and oculogyric crisis
Restlessness
Diarrhoea
Colic
Neuroleptic malignant syndrome

Usual dose range:

30-100 mg /24 hours – higher dose usually used by CSCI for delayed gastric emptying / peristaltic failure

Evidence

Palliative Care:

- Evidence for effectiveness in palliative medicine is limited - audit based (Bruera 1996) and small crossover study (Bruera 2000) looking at chronic nausea and dyspepsia in advanced cancer.
- Use in bowel obstruction: 2 studies (Fainsinger 1994, Ibister 1990): not clear as the value of the intervention, although suggestion that may be useful in patients with incomplete and non-colic terminal obstruction. On balance, trial up to 100mg/24 hours, via CSCI.

- Combining metoclopramide and anti-muscarinics: animal studies would suggest that anti-muscarinics do block the stimulating effect of prokinetics. (Schuurkes 1996)
No human studies measuring clinical outcomes

Chemotherapy related:

- Good evidence for its use to prevent acute emesis, effect is potentiated by dexamethasone

Diabetic gastropathy:

- Clinical syndrome of upper GI tract symptoms suggestive of upper motility disturbance. Prokinetic agents may be beneficial because of several actions: they accelerate delayed gastric emptying, relax fundus, and accelerate small bowel transit. Meta analysis (Strum 1999) and Cochrane review (Soo 2000) concluded that there is no convincing evidence that improvement in gastric emptying necessarily correlates with symptom relief.
- Established role in functional dyspepsia.
- Evidence for relief of nausea and post-prandial fullness

Post operative:

- Systematic review of randomized placebo controlled trials showed NNT to prevent early (0-6 hrs) PONV = 9.1 and late (0 – 48 hrs) = 10, but variable doses and routes used (Henzi 1999). NNH (extrapyramidal s/e) = 556
- Appears to be less clinical efficacy than 5HT3 antagonists, droperidol and Dexamethasone.

Conclusion

- Use primarily as prokinetic, eg in peristaltic dysfunction, delayed gastric emptying and cancer associated dyspepsia
- Good evidence for use in combination with corticosteroids for acute emesis associated with chemotherapy
- Trial in non-colic (incomplete) bowel obstruction
- Do not combine with potent antimuscarinic drug

DOMPERIDONE

Pharmacology

Dopamine (D2) receptor antagonist (no 5HT4 agonist - excitatory effect)
Doesn't cross blood-brain barrier

No parenteral form available

Suppository available (30mg PR = 10 mg po)

Onset of action: 30 mins

Plasma half-life: 14 hours

Duration of action: 8 - 16 hours -can be given twice a day

Usual dose

20 mg bd - qds

Evidence

- Evidence in diabetic gastroparesis from RTC (Patterson 1999) that domperidone 20 mg qds as effective as metoclopramide 10mg qds in resolving the symptoms of gastroparesis with less adverse CNS effects.
- Evidence for use to prevent emesis and improve patient compliance with chemotherapy (Bussink 2002)

Conclusion

- Useful when a prokinetic without extrapyramidal side effects is needed eg Parkinson's disease

5HT3 ANTAGONISTS

Pharmacology:

Serotonin (5HT3) is synthesized in the body from tryptophan at three main sites - intestinal wall (90%), platelets and CNS

5HT3 receptors found predominantly in GUT and CNS – area postrema, cortex and limbic regions

5HT3 antagonists block the amplifying effect of excess 5HT on vagal nerve fibres, and hence are of specific value where excess amounts of 5HT3 are released from the bodies stores eg following chemotherapy, damage to gut mucosa (radiotherapy, bowel obstruction) and in renal failure (leaky platelets).

Elimination half life (hours):

Granisetron 11.6

Ondansetron 5.6

Tropisetron 5.7

Palonosetron 37

Duration of action (hours):

Granisetron 24

Ondansetron 9 (consider tds dosage)

Adverse effects:

Headache

Constipation

Sedation and fatigue

Rarely extrapyramidal symptoms, dystonic reaction

Usual dose range:

Granisetron 1-3mg daily oral or SC

Ondansetron 8 – 24 mg/24 hrs 2-3 divided doses

Evidence:

Palliative Care:

- Small studies of ondansetron (8-24 mg / 24 hrs) (Currow 1997) and granisetron (3mg) (Porcell 1998) have shown 70-80% significant improvement in nausea and vomiting from multifactorial causes in patients with advanced malignancy or AIDS (failed on standard antiemetics, mostly in the terminal phase)
- Ondansetron and granisetron have been used subcut with no local adverse effects (Porcell 1998)

- Chronic renal failure: Small double-blind crossover study (10 patients) in uraemic patients with nausea and vomiting compared 10 mg metoclopramide iv with 8 mg ondansetron iv (single dose study) concluded ondansetron was superior to metoclopramide. (Ljutic 2002)

Chemotherapy and Radiotherapy related:

- Good evidence from randomised controlled trials for the use of 5HT₃ antagonists in the following situations:
 - Prophylaxis of acute chemotherapy induced nausea and vomiting (Jantunen 1997)
 - Radiotherapy induced emesis – recommended as prophylaxis with moderately or highly emetogenic radiotherapy regimens (Tramer 1998, Tonini 2003, Horiot 2004)
- Less effective in delayed nausea and vomiting

Post op:

- Proven clinical effectiveness for both established PONV and preventing PONV– several randomised trials and systematic review (Tramer 1997, Kazemi-Kjellberg 2001)

Other situations:

- Case series (n= 7) suggesting effective for nausea and vertigo associated with acute brainstem disorders – predominantly multiple sclerosis (Rice 1995)
- Small randomised study comparing single dose ondansetron, metoclopramide or placebo in children with gastroenteritis (12 patients in each group) concluded ondansetron was better than placebo (Cubeddu 1997)

Conclusion

- 5HT₃ receptor antagonists have a role in the management of nausea and vomiting caused by disruption of bowel mucosa, as well as a central action on the chemoreceptor trigger zone and the vomiting centre.
- Specific role in chemotherapy and radiotherapy related nausea and vomiting, and post-operatively
- Precise role in palliative care patients specifically remains unclear.
- May have more specific role in renal failure and bowel obstruction
- Sufficient anecdotal evidence to support its use when other antiemetics have failed or have resulted in significant side effects.
- High cost – trial for three days then discontinue.
- Majority of studies have not shown clinically significant differences in efficacy between the 5HT₃ receptor antagonists (Gregory 1998). However, granisetron has simplicity of once daily dosage and is metabolised exclusively via single CYP family (CYP3A), whilst ondansetron, tropisetron and palonosetron have multiple enzymatic pathways. Hence reduced risk of pharmacokinetic drug-drug interactions with granisetron (Gridelli 2004)
- NB Newer 5HT₃ antagonist – Palonosetron – stronger affinity for 5HT₃ receptor and markedly longer half-life (37hrs) (Grunberg 2003)

STEROIDS

Pharmacology:

Possible mechanisms of action:

1. Inhibition of central prostaglandin synthesis. Steroids reduce arachidonic release which will decrease prostanoid turnover. Prostanoids can induce vomiting directly and also sensitise to other emetics.

2. Reduce capillary permeability and cerebral oedema eg caused by brain radiotherapy and chemotherapy
3. Activation of tryptophan pyrrolase - shunts the metabolism of tryptophan away from 5 HT synthetic pathway.

Adverse effects:

Agitation, insomnia, euphoria
Increased appetite
Fluid retention
Dyspepsia
Raised blood sugar
Myopathy

Usual dose range:

Dexamethasone: 4 - 8mg orally / subcut (8 – 16 mg for raised intracranial pressure or bowel obstruction)
5 – 8 mg iv for prevention of CINV or PONV

Evidence:

Palliative Care:

- Malignant bowel obstruction - Cochrane review - ? have a role due to their anti-emetic, co-analgesic and anti-inflammatory effects.
3 methodologically sound, double blind, randomised, controlled trials (only involved 89 patients), 7 other reports. “Trend for evidence that 6 – 16 mg dexamethasone iv may bring about resolution of bowel obstruction”. Suggests 4 –5 days trial of Rx. Low incidence of side effects. Does not seem to affect survival or mortality. NNT = 6. NB: spontaneous resolution of obstruction in the placebo arms of the trials 33 – 60 %. (Feuer D.J. 2000)
- Chronic nausea – RCT (n=51, patients with advanced cancer taking metoclopramide 60mg od orally) failed to demonstrate that dexamethasone was superior to placebo (Bruera 2004) although limitations in the study.

Chemotherapy / Radiotherapy related:

- Good evidence for effectiveness in :
 1. Acute and delayed chemotherapy induced emesis (Apro 1991, Ioannidis 2000)
 2. Prevention of post radiotherapy nausea and vomiting (Kirkbride 2000)
- Frequently used in combination with metoclopramide or 5HT3 antagonists, enhancing their effect

Post operative nausea and vomiting:

- Proven effectiveness compared to placebo
- Enhances effects of other anti-emetics eg 5HT3 antagonists
- Systematic review confirms above, decreases risk especially of late onset PONV. No significant adverse effects. (Henzi 2000)
- In combination with 5HT3 antagonist: - dexamethasone as effective as droperidol (Habib 2004)

Conclusions

- Dexamethasone is effective antiemetic for chemotherapy induced and post-operative nausea and vomiting. Dose up to 8 mg / day, no benefit from higher doses (Drapkin 1982, Elhakim

2002, Italian Group 2004) It augments the effect of metoclopramide and 5HT3 antagonists. (ASHP 1999)

- Use for raised intracranial pressure (dexamethasone 8-16mg)
- 5 day trial for bowel obstruction
- Consider trial in other situations eg intractable vomiting as short-term adjunct to other anti-emetics

HYOSCINE

Pharmacology

Antimuscarinic properties, therefore antisecretory and smooth muscle relaxant

Hyoscine butylbromide less lipid soluble therefore does not cross the blood-brain barrier, and less well absorbed from gut

	<u>Hyoscine butylbromide</u>	<u>Hyoscine hydrobromide</u>
Oral bioavailability	10%	60-80% sl
Onset of action	1-2h po, <10mins sc/im/iv	10-15 min sl, 3-5 mins sc
Plasma halflife	5-6h	5-6h
Duration of action	2h in healthy volunteers, (longer in moribund patients)	15 mins as antispasmodic, 1-9h antisecretory

Adverse effects

Blurred vision

Dry mouth

Heartburn

Constipation

Urinary hesitancy and retention

Cardiac arrhythmias

Sedation and delirium (hydrobromide only)

Contra-indicated in acute closed angle glaucoma (except in moribund patients)

Usual dose:

Hyoscine hydrobromide :

- Injection 300- 400mcg stat, and repeated prn. Max 1200mch/24h in CSCI
- Scopoderm patch 1mg/72 hours
- Tablet (Kwells) 300mcg sl

Hyoscine butylbromide :

- Injection 20mg stat, max 300mg/24h via CSCI
- Tablet (Buscopan) 20mg QDS

Evidence:

Palliative care: Bowel obstruction

- Case series describe the use of hyoscine butylbromide in bowel obstruction, resulting in reduction of volumes in nasogastric secretions, and also reduction in nausea and vomiting (De Conno et al 1991)

- Randomised trials comparing hyoscine butylbromide with octreotide show the latter is more effective and produces more rapid relief of symptoms (see octreotide entry) All effects attributed to anti-secretory properties of drugs.

Chemotherapy and radiotherapy

- No studies found

Post operative nausea and vomiting

- Randomised controlled trials (n=50 and 66) comparing scopoderm versus placebo on PONV in ear surgery (Honkavaara 1995, 1996) demonstrate significant improvement in nausea, retching and vomiting over 24hours post op with scopoderm and less need for breakthrough medication. Patients with a past history of motion sickness benefited most from hyoscine
- Other RCT's comparing scopoderm with placebo following gynaecological surgery (Semple 1992, Uppington 1986) showed significant reduction in PONV with scopoderm, but still a high incidence (68%, 78%).
- Main side effects from above studies were sedation, blurred vision and xerostomia
- Other studies have demonstrated no significant improvement (Koski 1990, Gibbons 1984, Tigerstedt 1988)

Motion sickness

- Double blind crossover study (n=18) of hyoscine v zamifentacin (M3 & M5 receptor antagonist) v placebo po given 1 hour prior to a motion sickness test showed both drugs to be equally effective over placebo (Golding JF 1997)
- Cross over study demonstrated 600mcg hyoscine was significantly better than 30mg cinnarizine (Stugeron) or placebo in preventing vomiting following a motion challenge (Pingree BJW 1989)

Conclusions:

- Proven anti emetic for motion sickness
- Some evidence of mild efficacy in post op nausea and vomiting
- Proven anti secretory drug, therefore with anti emetic properties in malignant bowel obstruction
- Trials show greater efficacy of alternative anti emetic in head to head studies eg metoclopramide / octreotide

OCTREOTIDE

Pharmacology:

Synthetic analogue of somatostatin (an inhibitory hormone found throughout the body), with longer duration of action.

Actions:

1. Effect on GIT:
 - a. Inhibits secretion of sodium, chloride & water into the bowel lumen (via blockage of hormonal mediators eg VIP)
 - b. Stimulates intestinal absorption of water & electrolytes
 - c. Decreases gut motility from stomach to large bowel
 - d. Slows gastric emptying, gastric acid secretion and ↓ splanchnic blood flow
 - e. Decreases lower oesophageal sphincter pressure

2. Effect on hypothalamus/pituitary: inhibits release of growth hormone, TSH, prolactin, ACTH

Half life 100mins

Duration of action 12 hours

Adverse effects:

Dry mouth – inhibits salivary flow. May improve after 24 hours

Flatulence

Hyperglycaemia after meals

Usual dose:

Dose: 300-600mcg / 24 hours either by CSCI or bd injections

Slow release preparations also available: sandostatin LAR, lanreotide

Evidence:

Bowel obstruction:

- Several case series (n = 13 –26) describe use in bowel obstruction (Khoo 1994, Mercadente 1993 & 1995, Mangili 1996)
- Often used in combination with other antiemetics eg haloperidol
- Randomised trials of octreotide vs hyoscine butylbromide show both reduce secretions, but octreotide was more effective and quicker acting (within 48 hrs). Doses used: octreotide 0.3 mg (Riapamonti 2000, Mercandante 2000) or 0.6-0.8mg (Mystakidou 2002), hyoscine butylbromide 60-80mg.

Conclusion:

- Lack of quality evidence
- Octreotide at dose 300 – 1200 mcg per 24 hours in patients with inoperable bowel obstruction may reduce volume and frequency of vomiting within 2-3days of commencing therapy.
- The effect can be additional to that of haloperidol
- Well tolerated

BENZODIAZEPINES

Pharmacology

Bind to specific receptors in the CNS- enhance the effect of GABA (inhibitory neurotransmitter)

Effect on function of other neurotransmitters (serotonin, catecholamines, etc;)

Site of action: Cerebral cortex, reticular activating system, limbic system. Lesser effect on brainstem and spinal cord

Anti-emetic effect due to: ?anxiolytic effect

?? GABA receptor antagonism or inhibition of dopamine release

Pharmacokinetics – considerable variation

Strongly bind to plasma proteins and are lipid soluble, accumulating in body fat

Excreted as Glucuronide conjugates in the urine

Plasma half-lives:

long t $\frac{1}{2}$ -> anxiolysis and anticonvulsant

med t $\frac{1}{2}$ -> hypnosis and anxiolysis

short t $\frac{1}{2}$ -> premed and sedation

Clonazepam, Diazepam

Oxazepam, Temazepam, Lorazepam

Midazolam, Triazolam

Lorazepam:

Marked amnesic properties

Dose 0.5 - 4 mg

Peak serum levels 2 hours

Plasma half-life 12 hours

Adverse effects:

Dose dependant drowsiness

Impaired psychomotor skills

Hypotonia

Physical and psychological dependence – worse with short acting members

Elderly and patients with liver disease particularly susceptible to side effects

Evidence

Chemotherapy induced:

- Most studies use lorazepam
- Randomised double-blind studies show addition of lorazepam to ondansetron and steroid (Harousseau 2000), metoclopramide (Gordon 1985) or prochlorperazine (Bishop 1984) reduces incidence/severity of nausea and vomiting
- Most studies: > 80% patients sedated (mild/ moderate, easily aroused)
- Sedation not necessarily undesirable

Anticipatory nausea and vomiting (ANV):

No effective pharmacological approach to ANV, best to prevent it happening

Benzodiazepines and some behavioural therapies have been used with success.

Models of ANV:

1. Example of Pavlovian conditioning -innocent stimuli triggering the physiological response, several courses of chemo needed. Therefore agent causing temporary lack of recall (eg lorazepam) prevents memory imprint that is part of the learning process and may be of value.
2. Result of emotional state of anxiety that is conditioned to external cues. Is not a conditioned reflex directly

It therefore seems that patients who have not remembered vomiting or those who are not anxious about it would be less likely of developing ANV

Post-op:

- Randomised double-blind studies demonstrate positive effect of midazolam on PONV resistant to standard antiemetics (Di Florio 1999), and also when used peri-operatively to prevent nausea and vomiting (Heidari 2004, Sanjay 2004)

Conclusion

- Significantly reduce nausea and vomiting as adjunct to other anti-emetics in patients receiving cytotoxic therapy.
- Useful in anticipatory nausea and vomiting

- May be useful in patients with refractory nausea and vomiting where sedation is a desired effect
- Possible role in combination with other antiemetics where side effects are problematic eg extrapyramidal reactions

CANNABINOIDS

Pharmacology

Over 300 compounds in marijuana

Nabilone is only licensed cannabinoid in UK - 2nd line treatment of nausea and vomiting secondary to cytotoxic chemotherapy

Delta 9THC is one of the active compounds used in USA (Dronabinol) – trials occurring in UK

Action: 2 cannabinoid receptors identified CB1 and CB2 – in brain and periphery

Adverse effects:

Sedation

Psychomimetic - agitation, intoxication,

Clumsiness, dizziness,

Dry mouth

Lowered blood pressure

Increased heart rate

Evidence:

Palliative Care:

- Case reports in advanced cancer (Gonzalez-Rosales 1997) and AIDS (Flynn 1992)

Chemotherapy / radiotherapy related:

- Most studies done in 80's before newer antiemetics available
- Quantitative systematic review for CINV: 30 randomised comparisons of cannabis with placebo or antiemetics (1366 patients). Oral nabilone, oral dronabinol (tetrahydrocannabinol), and intramuscular levonantradol were tested. No cannabis was smoked. Cannabinoids were more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride: number needed to treat 6 for complete control of nausea; NNT 8 for complete control of vomiting. (Tramer 2001)
- Has been used in radiotherapy induced emesis (Priestman 1984). Possibly equipotent to metoclopramide, but causes more side effects, especially if on opioids or in patients with liver mets

Post-operative:

- Prospective double-blind study (n = 60) in PONV (hysterectomy) – no significant difference compared with metoclopramide (Lewis 1994)

Conclusion

- Some evidence re its effectiveness
- Significant adverse effects

- May have a role in uncontrolled nausea and vomiting, which hasn't responded to established antiemetics

ACUPUNCTURE / ACUPRESSURE

Thought to work peripherally and centrally by stimulating small myelinated nerves, and by causing release of natural endogenous opioids and neurotransmitters eg serotonin
Most common points used are P6 and ST36

Evidence:

Palliative Care:

- Little evidence in terminally ill patients with nausea and vomiting not associated with chemotherapy.
- One review article (Pan 2000) looking at use of complimentary medicine in Palliative Care identified only one relevant study that evaluated nausea and vomiting in a hospice setting. This small study (6 patients) - no difference between acupressure wrist band, placebo band and no band.

Chemotherapy related:

- Several studies (eg , Shen 2000, Josefson2003, Johnstone2002, Dundee1989), but not all studies use adequate sham control
- 1 study (Shen 2000) - Women with breast cancer, myeloablative chemotherapy-induced emesis. Compared electroacupuncture (n=37) vs. minimal needling and mock electrical stimulation (n=34) vs. antiemetic alone (prochlorperazine) (n=34) in the control
 - Once daily adjunctive electroacupuncture significantly reduced the number of emesis episodes occurring during the five days of chemotherapy - not sustained during the follow up period (when both chemo and acupuncture were completed).
 - Mock needling group also had significantly reduced number of emesis episodes compared with the anti-emetic alone group, although this effect was not as great as for the electroacupuncture group.
- Acustimulation wristbands may be effective (Roscoe 2002, Treish2003).

Peri-operative:

- The majority of studies focus on established post-operative nausea and vomiting
- Most studies were on well defined population groups, others looked at more general settings such as paediatric recovery (Wang 2002)
- Modes of administration ranged from traditional acupuncture to P6 point injections to electroacupuncture.
- Most studies report some kind of benefit from use of acupuncture. The less well controlled studies reported reduction in emetic episodes as well as nausea although this was not reproduced in a larger sham-controlled study which found a reduction in nausea scores but not in actual emesis (Rusy 2002).
- Comparative studies with anti-emetics report that P6 acupoint injection is as effective as droperidol in early but not late (24hrs or later) nausea and vomiting (Wang 2002) and that

the combination of ondansetron and electroacupuncture is more effective than either used alone (White 2002).

Other situations:

- Systematic review of interventions for nausea and vomiting in early pregnancy concludes that results from trials of P6 acupuncture are equivocal. (Jewell 2003)
- Small study (n=25) in motion sickness (normal subjects, rotating drum (Stern 2001). Acuband (acupressure) reduced symptoms compared with control (no band), but effect seen when band applied to both P6 point and further up the arm.

Conclusion

There is evidence supporting the use of acupuncture for the treatment of post-operative and chemotherapy-induced nausea and vomiting, but little evidence in terminally ill patients with nausea and vomiting not associated with chemotherapy

Questions remain with regards to the technical application of acupuncture for nausea and vomiting

Which type of acupuncture?

Which site?

How often?

GINGER

Pharmacology:

Active ingredient not known

Composition of formulations may vary widely according to different regions of origin and postharvesting factors

Evidence:

Palliative Care:

- No evidence for its use in palliative care setting

Chemotherapy related:

- One randomized double-blind study suggested powdered ginger root was as effective in reducing nausea and vomiting as metoclopramide but not as effective as ondansetron. (Sontakke 2003)

Post operative:

- Few randomized controlled trials with contradictory results (Pongrojapaw 2003, Eberhart 2003)
- Systematic review of the use of ginger to prevent PONV (Morin 2004) concluded that 11 patients must be treated with ginger for one additional patient to remain free from PONV, and that ginger was not a clinically relevant anti-emetic.

Pregnancy:

- Many small studies – suggest is useful in reducing first trimester nausea scores and the number of vomiting episodes experienced. (Vutyavanich 2001, Jewell 2003)

- Onset of anti-emetic effect varied from immediate onset to over a week.
- Dose of ginger ranged from 1-1.5g of dried ginger equivalent
- Differing formulations - capsules of dried ginger, ginger extract, ginger syrup.
- Uncertainty re reliability of data – small studies, variable outcome measures, publication bias

Conclusion:

- May have value as anti-emetic herbal remedy
- Clinical data to date insufficient to draw firm conclusions
- Need to establish optimal dose, formulation and frequency of administration.

Appendix 1:

OLANZAPINE

Pharmacology:

Atypical antipsychotic agent of thienobenzodiazepine class.

Has affinity for multiple neurotransmitter receptors, including dopaminergic (D₁, D₂, D₃, D₄), serotonergic (5-HT_{2a}, 5-HT_{2c}, 5-HT₆, and to a lesser extent 5-HT₃), adrenergic (alpha 1), histaminergic (H1), and muscarinic (m1, m2, m3, m4) receptors.

Orodispersible tablet (Velotab) – dissolves in mouth but not absorbed from mouth.

Can also be dissolved in water, orange juice, apple juice, milk, or coffee.

Also parenteral form

Adverse effects:

The common side effects reported with olanzapine include somnolence, postural hypotension, constipation, dizziness, restlessness and weight gain.

Evidence:

- Several single case reports – advanced cancer and palliative care (Jackson 2003)
- Open label pilot study – advanced cancer, opioid analgesics (15 patients), doses 2.5 – 10 mg od. 5mg and 10mg doses both led to significantly reduced nausea (Passik 2002)
- Retrospective chart review: 28 patients who received olanzapine (2.5 or 5 mg bd) for prevention of delayed emesis chemotherapy. Not compared with other regimens but rates of N+V less than expected (Passik 2003)

- Phase I study for prevention of delayed chemotherapy induced emesis concluded olanzapine 5-10 mg od may be useful (Passik 2004)

Note on CSM warning:

The CSM has advised that there is clear evidence of an increased risk of stroke in elderly patients with dementia who are treated with risperidone or olanzapine. A pooled analysis of randomized placebo controlled trials of olanzapine in elderly patients with dementia has shown an increased risk of stroke (approximately 3-fold) and a 2-fold increase in all cause mortality.

The mechanism by which these drugs are associated with stroke is unclear. Although some patients with dementia may have underlying vascular disease, the risk is not confined to this group, and although most of the evidence causing concern comes from patients with dementia, the risk may not be confined to use in this indication and should be considered relevant to any patient with a history of cerebrovascular disease or relevant risk factors.

The result of this warning has led to a decline/cessation in use of both olanzapine and risperidone in the treatment of elderly people across Yorkshire for both licensed and unlicensed indications. Therefore as palliative care specialists we should consider very carefully if/when we recommend olanzapine.

Conclusion:

Given the CMS warnings and poor quality evidence olanzapine is not routinely recommended, however it may be worth considering if no other anti-emetic has been effective or tolerated.

Appendix 2:

DROPERIDOL

Butyrophenone

Similar actions to haloperidol

Randomised-controlled trials confirm effectiveness as antiemetic post-operatively and for nausea and vomiting associated with chemotherapy or morphine. Efficacy post op and associated with chemotherapy is improved if combined with 5HT3 antagonist and corticosteroid.

Not featured in BNF as anti-emetic or neuroleptic. Has been “black box” warning by FDA in America – prolongs QT interval – hence linked to cardiac arrhythmias and risk of cardiac arrest.

Conclusion:

In view of potential toxicity, myriad of alternatives and lack of information in palliative care patient group, cannot be recommended for routine use.

Appendix 3:

ERYTHROMYCIN

NB Not licenced as antiemetic

Pharmacology:

Prokinetic

Motilin agonist - action limited to stomach

Tolerance develops within a few days

Macrolide compounds with no antibacterial properties but with prokinetic properties currently being developed

Adverse effects:

Poorly tolerated

Crampy abdominal pain, diarrhoea - ? due to change in intestinal flora due to its antibiotic effect

Can cause nausea and vomiting

Conclusion:

- Systematic review of all trials of erythromycin in gastroparesis (Maganti 2003) concluded that although clearly a prokinetic, limited data exists in its use as a treatment. All trials were poorly designed. Not currently recommended for use

Appendix 4:

NK1 ANTAGONISTS

The NK1 antagonist *Aprepitant* has been licensed by the FDA for the prevention of both acute and delayed CIMV. It is licensed in the UK as an adjunct to dexamethasone and a 5HT₃ antagonist in preventing acute and delayed nausea and vomiting associated with cisplatin-based chemotherapy.

Pharmacology:

- Substance P is a tachykinin found in brainstem neurones and is involved in pain, depression, anxiety, inflammation and nausea and vomiting. It is the preferred ligand of the NK1 receptor. NK1 receptors have been shown to be involved in both acute and delayed onset chemotherapy-induced nausea and vomiting (CIMV).
- Main pathway of elimination is by the cytochrome p450 isozyme CYP3A4 - basis for drug interactions eg dexamethasone, warfarin
- Terminal half-life is between 9 and 13 hours.

Adverse effects:

Generally well tolerated.

Most common adverse events are asthenia, fatigue, anorexia, constipation, diarrhoea, hiccups, dyspepsia, headache.

Evidence:

- Improves complete response rate in acute CINV in patients receiving highly emetogenic chemotherapy when added to standard regimen of 5HT₃ and dexamethasone
- Improves complete response rate in delayed CINV when used in combination with dexamethasone compared with dexamethasone alone.
- No studies specifically looking at the role of NK1 antagonists in the management of nausea and vomiting in palliative care patients.

Appendix 5: DRUG INDUCED SYNDROMES (DOPAMINE ANTAGONISTS)

Neuroleptic Malignant Syndrome

Four primary features:

- Autonomic lability (↑ heart rate, ↑ respiratory rate, excess sweating)
- Hyperthermia without other cause
- Extrapyrimal syndrome (cogwheel or lead pipe rigidity)
- Encephalopathy (altered consciousness)

+/- leukocytosis, ↑ CPK.

May mimic severe parkinsonian reaction, infestation or advancing malignancy. Onset usually abrupt and fulminant (24-72 hrs). 20-30% mortality.

Treatment - withdraw drug, control fever

Dantrolene and centrally active dopamine agonist eg bromocriptine. In extreme cases competitive neuromuscular blocking agent is effective.

Consider benzodiazepines

Acute dystonic reactions

Eg haloperidol, metoclopramide

Sustained abnormal postures or muscle spasms that develop within 7 days of starting antipsychotic medication.

Usually subsides within 24hrs of discontinuing the drug.

Treated with procyclidine 5-10mg IV

Oculogyric crisis – can add clonazepam

Appendix 6: PROBLEMS in EVALUATING STUDIES of ACUPUNCTURE

- A lot of reviews criticise the methodology used in trials of acupuncture.
- Clinical evidence of the efficacy of acupuncture is more difficult to assess than for other, more conventional, treatment modalities. This is partly because of the issue of using a comparable standard or control and partly because of the difficulty of blinding to minimise performance bias.
- There is a known high placebo effect from acupuncture which may complicate any detection of any intervention-control difference.
- There are several types of trial design in the earlier literature
 - Acupuncture vs. untreated.
This may show that acupuncture is more efficacious than doing nothing but does not discriminate the effect from placebo or non-specific treatment effect
 - Acupuncture vs. standard biomedical treatment.
This assumes that the standard treatment has been shown to be more efficacious than placebo (not always the case) so that if acupuncture produces effects equal or greater than those of the standard treatment it can be assumed to be more efficacious than placebo.
 - Acupuncture vs. comparable treatment modality (putatively ineffective or sham manipulation) e.g. acupuncture at a putatively ineffective site or use of a blunted needle or inactive electrodes.

The gold standard, but not without problems. One difficulty is that there is no consensus on what constitutes the appropriate sham control and it is also difficult to maintain blinding in such studies. The ideal sham control should be inert, identical in appearance and sensation and without non-specific physiological effects

- There is also heterogeneity of acupuncture techniques, including:-
 - Conventional Acupuncture. The practice of piercing specific peripheral nerves with needles
 - Electroacupuncture. This uses low frequency electrically-stimulated needles
 - Acupressure. This uses similar principles but is administered with local pressure from fingers or pressure bands

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