Levomepromazine for nausea and vomiting in advanced cancer

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Levomepromazine (previously known as methotrimeprazine), despite virtually no high quality scientific data to support its use, has become a very popular antiemetic for use in patients with advanced cancer. This article considers the reasons for this.

Nausea and vomiting are common and unpleasant symptoms in advancing cancer, nausea affecting about 30% and vomiting affecting about 20% of patients seen by hospice and hospital palliative care teams (Edmonds et al, 1998; Kai and von Gunten, 1998). They affect the patient's quality of life and morale as well as leading to other symptoms such as poor appetite. Delayed gastric emptying associated with nausea may cause poor absorption of oral medication leading to poor control of other symptoms. Current treatments are not fully effective. EEC directive 92/27 EEC requires use of the recommended international non-proprietary name for medical substances. Methotrimeprazine will now be known as levomepromazine. Low dose levomepromazine is becoming more widely used in palliative care despite the fact that hardly any good quality clinical research has been published. This may be because levomepromazine works very well and high quality research in palliative care is difficult to undertake.

LEVOMEPROMAZINE

Levomepromazine is a phenothiazine, like promazine or chlorpromazine. It has been used as an antipsychotic, in animal and human anaesthesia, as a sedative drug for terminal restlessness and as an analgesic, although it has never been popular in the UK for analgesia. It is also emerging as an effective 'broad spectrum' antiemetic.

Levomepromazine seems more sedative and more likely to cause postural hypotension than chlorpromazine; these probably prevented it from realizing its full potential as an antipsychotic. Oral administration results in effective concentrations in the blood in less than 1 hour and elimination is slow enough to allow once-daily dosing (Dahl, 1976). Oral bioavailability is about 50%.

Levomepromazine is an effective antagonist at dopamine (D_2), serotonin ($5HT_2$), histamine (H_1) and muscarinic cholinergic receptors. Levomepromazine is not active at the $5HT_3$ receptor, unlike newer antiemetics like ondansetron (Link pharmaceuticals, data on file).

CENTRAL CONTROL OF VOMITING: A RATIONALE FOR ANTIEMETIC CHOICE?

Vomiting is produced by intestinal smooth muscle and thoracic and abdominal striated muscle activity generated by the vomiting centre in the medulla. This centre is less circumscribed than was once thought and is sometimes referred to as the emetic pattern generator, implying no discrete single location in the brainstem. The vomiting centre receives afferent input from several sources:

- Chemoreceptors in the area postrema (the chemoreceptor trigger zone, CTZ). This exerts a tonic influence on the vomiting centre maintaining sensitivity to other stimuli as well as producing emesis in response to bloodborne toxins such as drugs, notably opioids. The CTZ projects upon the vomiting centre via D_2 and probably $5HT_3$ neurones
- Vagal afferents project from gut chemoreceptors, possibly via $5HT_3$ fibres
- Vestibular afferents project via muscarinic cholinergic and histaminergic (H_1) fibres, the mechanism of motion sickness
- The cerebral cortex projects onto the vomiting centre, probably via GABA, H_1 and unknown subtypes of 5HT neurones. These connections mediate the vomiting caused by raised intracranial pressure and fear or anxiety.

The vomiting centre itself is rich in $5HT_2$ receptors.

Dopamine (D_2) antagonists (e.g. prochlorperazine) are effective antiemetics, as are antihista-

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mines (H_1, e.g. cyclizine) and antimuscarinics (e.g. hyoscine). Recently, $5HT_3$ antagonists have been used as antiemetics (e.g. ondansetron). Matching the supposed emetic stimulus to the drug most likely to block that stimulus is often used as a rationale for antiemetic selection, e.g. prochlorperazine for opioid-induced emesis and cyclizine or hyoscine for motion sickness. (Attractive as this is, there is no real evidence that it leads to more effective antiemetic strategies.)

Despite this current best practice is to match therapy to the cause of nausea or vomiting and the condition of the patient. Treating the cause may be simple and effective, e.g. correction of digoxin toxicity. However, if the patient is in the dying phase of their illness, it may be more appropriate to treat symptoms medically; effective antiemetics are crucial for this.

Current treatment of nausea and vomiting in advanced cancer mainly uses haloperidol, cyclizine or haloperidol plus cyclizine. In cases with a clear cause, the appropriate antiemetic is often effective and should be the drug of first choice. However, in many patients it is difficult to establish the cause, or the cause may be multifactorial (*Table 1*). In these patients an antiemetic with a wider spectrum of activity may be appropriate.

A BROAD SPECTRUM ANTIEMETIC?

Since 1980 the potent antiemetic properties of levomepromazine in chemotherapy patients have been recognized (Higi et al, 1980). In palliative care use of levomepromazine as a sedative for terminal agitation (for which it was and is widely used) produced effective control of vomiting (Oliver, 1985). Old work on levomepromazine as an analgesic suggested potent antiemetic effects (Minuck, 1972). Despite this there is very little published work on the drug as an antiemetic.

Twycross et al (1997) are, however, in no doubt that, even at very low doses, levomepromazine is a potent antiemetic. Their discussion on the mechanism of action begins 'Given the incontrovertible clinical experience...'. Many palliative care physicians share this view and low dose levomepromazine is now recommended in textbooks on symptom control (Regnard and Tempest, 1998; Kaye, 1997; Twycross, 1997). Low dose levomepromazine is becoming more popular and widely recommended, despite the lack of objective data. This is similar to when spinal opioids became popular in the 1980s far ahead of the literature and is occurring for the same reason: it is obvious that levomepromazine works well in clinical practice.

Being a potent D_2, H_1, $5HT_2$ and muscarinic receptor antagonist it seems reasonable to view levomepromazine as a compound which blocks most of the receptors known to be involved in vomiting, so its antiemetic effects are not unexpected. (It is not clear whether levomepromazine's antiemetic actions are chiefly caused by $5HT_2$ blockade or combined block of D_2, H_1, $5HT_2$ and muscarinic receptors.) If selection of antiemetics by the nature of the emetic stimulus has any validity, then it would be reasonable to use levomepromazine for vomiting of multiple or unknown causes and as the second-line drug for vomiting refractory to first-line treatment. Because levomepromazine is effective as an antiemetic at much lower doses than antipsychotic or sedative doses, it does not have serious side-effects. It is crucial that high quality clinical trials are undertaken soon to confirm or repudiate this clinical belief with confidence.

PRACTICAL USE

Levomepromazine is presented as a white scored 25 mg tablet or a 25 mg/ml injection. The duration of action is 12–24 hours, with onset of action in 30 minutes, making it suitable for once-daily administration orally or subcutaneously. It can also be given by continuous subcutaneous infusion

TABLE 1.
Vomiting in advanced cancer

Causes which may be directly treatable	Constipation	
	Ascites	
	Raised intracranial pressure	
	Pain	
	Anxiety	
	Hypercalcaemia	
	Hyponatraemia	
	Renal failure	
	Gastric stasis	
	Infection	
	Drug toxicity	Carbamazepine
		Digoxin
		Theophylline
		Non-steroidal anti-inflammatory drugs
		Corticosteroids
	Peptic ulcer	
Causes requiring antiemetics as first-line treatment	Any directly treatable cause where the patient is deemed too ill for first-line treatment to be appropriate	
	Bowel obstruction	
	Hepatomegaly	
	Tumour load	
	Radiotherapy	
	Chemotherapy	
	Opioids	

(CSCI). The antiemetic dose widely used in current hospice practice is 6.25–12.5 mg orally or 2.5–12.5 mg subcutaneously in a single daily dose, although if a CSCI is being used levomepromazine can be added to this. Oral doses are usually given in the evening to take advantage of possible sedative effects, although these are not common. These doses are considerably less than the antipsychotic dose of levomepromazine (50–200 mg per day initial dose) and much less than the amount of drug in a single tablet or vial.

Patients with nausea or delayed gastric emptying may require parenteral medication initially to improve availability and to allow the stomach to empty before conversion to oral treatment.

WHY LEVOMEPROMAZINE, NOT COMBINATION THERAPY?

Many patients have multiple aetiologies for their nausea and vomiting, or the cause cannot be identified. Cyclizine or haloperidol alone may not control their symptoms and the standard advice has been to combine the two, blocking most of the receptors in the vomiting pathways. An antiemetic with a wider receptor affinity may provide effective control in a single preparation.

Patients with advanced cancer are often already on complicated medication regimens for other conditions involving many tablets. A regimen that requires a single daily dose of antiemetic may produce greater compliance. A cyclizine and haloperidol regimen usually requires at least four tablets a day, whereas a single or twice daily dose of levomepromazine, if effective, is much simpler.

CONTINUOUS SUBCUTANEOUS INFUSIONS

The practical problem in CSCI is the stability of mixtures with many components (often judged by the presence or absence of a precipitate). Levomepromazine and diamorphine appear stable in solution and can be mixed in a syringe driver. Cyclizine and diamorphine in solution are less stable and may crystallize, especially if the diamorphine dose is increased. Levomepromazine appears compatible with other drugs that may be required in the terminal phase of illness, e.g. hyoscine, and can be used in higher doses if terminal agitation is a problem and sedation is required.

KEY POINTS

- Levomepromazine is an effective 'broad spectrum' antiemetic at doses that cause few side-effects.
- Levomepromazine has a long duration of action, enabling once-daily dosing.
- Levomepromazine is suitable for use in a subcutaneous infusion by syringe driver alone or with most other commonly used syringe driver drugs.

Because of the question of stability, some units prefer not to use more than two drugs in any syringe driver, and levomepromazine will overcome this problem if a combination of only an opioid and antiemetic is required.

SIDE-EFFECTS

At the doses recommended above, side-effects other than mild sedation are uncommon with levomepromazine but higher (antipsychotic) doses may cause significant sedation or postural hypotension. Cyclizine is, of course, also sedating in antiemetic doses. Levomepromazine can cause skin irritation when delivered by CSCI, although it is less likely at antiemetic doses. Dilution to twice the volume in saline is suggested by the manufacturers if a single subcutaneous dose is being given and dilution to the maximum volume practicable in the syringe if a CSCI is being used.

CONCLUSION

Nausea and vomiting is an unpleasant and common problem. Drugs currently used to treat it are not always satisfactory and are often costly. Among those who have used it there is almost universal acceptance that low-dose levomepromazine is an effective, cheap and safe antiemetic. It is widely recommended by different experts, especially for vomiting of mixed aetiology or where first-line antiemetics are ineffective. Scientific evaluation of this drug is long overdue. The problem is that those who use it regularly might feel reluctant to randomize their patients to other, apparently less effective, treatments. HM

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