CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Palliative medicine: Old dogs and new tricks

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ABSTRACT

In palliative medicine, many older drugs can be used for off-label indications, either to augment the action of approved drugs or to substitute for approved drugs that fail to provide relief.

THE STANDARD DRUGS used in palliative medicine—eg, analgesics, antiemetics, corticosteroids, psychoactives—serve us well. But tolerance and lack of response to standard therapies have led clinicians to explore off-label uses. Finding new uses for older drugs is an important part of palliative care.

TREATMENTS FOR PAIN

Methadone

Despite its undeserved bad reputation, due in part to its use in the addict population, methadone may soon be second only to morphine in the treatment of pain in patients with advanced cancer. Methadone offers several advantages over morphine:

- A lack of toxic neuroactive metabolites means it causes less myoclonus than morphine
- It has a serotonin and norepinephrine uptake-inhibiting activity that potentiates the descending spinal pathway of pain inhibition (Morphine neither has monoamine reuptake inhibiting activity nor does it significantly block N-methyl-D-aspartate [N-MDA] activity.)
- Its oral bioavailability is 80% vs 30% for morphine, and its half-life is 17 to 120 hours vs 2 to 4 hours for morphine
- Multiple routes of administration are possible, and rectal absorption is equivalent to oral absorption
- It is a mu receptor agonist, but it also blocks the N-MDA receptor, which is thought to be responsible for opiate tolerance or resistance.

Changing over from morphine to methadone requires careful titration to ensure that the dose of methadone given provides an equal level of analgesia without adverse effects. The methadone/morphine ratio is inversely proportional to the initial dose of morphine. The initial dose is 10% of the daily oral morphine equivalent up to 300 mg. The maximum single initial dose is 30 mg given every 3 hours as needed. After day 2 or 3 the methadone requirement will drop and will be at steady levels at 4 to 5 days.

Methadone is active in neuropathic pain and refractory pain and should be used before considering spinal analgesia or neurodestructive procedures.

Valproate for pain plus depression

Valproate is well-known in the treatment of partial seizures, generalized seizures, bipolar schizoaffective disorders, and migraine pain. Palliative care specialists now use it to treat neuropathic pain and depression simultaneously.

Valproate offers several advantages over traditional tricyclic antidepressants in palliative care:

- It is not anticholinergic and so does not cause dry mouth or constipation
- It does not affect cardiac rhythm
- It does not affect the white blood cell count, frequently a problem with carbamazepine
- It can be dosed once nightly.

Many older drugs can be used for off-label indications

*The author discusses off-label uses of medications.

On the other hand, valproate is metabolized via the hepatic cytochrome P450 system, so the risk of interactions with other antidepressants and antiseizure drugs is high.

Gabapentin

Gabapentin, used mainly to treat seizures, would probably be the number one drug for neuropathic pain in palliative medicine if not for its high cost. In a recent study, 20 of 22 patients with neuropathic pain due to advanced cancer reported improvement when treated with a mean of 1 g per day.

Gabapentin's chief advantage over valproate is that it is not metabolized via the hepatic cytochrome P450 system, and therefore the risk of drug interactions is low. In addition, gabapentin does not cause arrhythmia and is neither myelosuppressive nor anticholinergic. On the other hand, gabapentin causes sedation and dizziness and must be given several times a day. Its clearance depends on renal function; hence, doses will need to be adjusted downward with reduced renal function.

Cannabinoids for pain and nausea

Changing from morphine to methadone requires careful titration

In the 1970s, cannabinoids were developed and were found to have modest antinauseant and analgesic effects. But because high doses caused dysphoria in older patients, they were an unlikely treatment in the palliative medicine setting, where most patients are elderly. Low doses of 2.5 mg twice to three times daily are tolerable in older patients and are effective in relieving nausea without dysphoria.

In addition, cannabinoids are experiencing a resurgence of interest as a treatment for both neuropathic pain and nausea. The identification of the cannabinoid receptor CB1 has spurred interest in the analgesic potential of cannabinoids. The CB1 receptor appears to mediate analgesia through indirect antagonism of the N-MDA receptor. There also appears to be synergy between CB1 and the mu receptor.

As for its antinausea potential, we now know that cannabinoid receptor activation blocks propulsive movements: ie, it has an antikinetic effect that may be beneficial for patients with bowel obstructions or bowel metastases.

Methylphenidate to enhance opiate analgesia and cognition

Methylphenidate, widely used as a psychostimulant in children with attention deficit disorder, is now being used in palliative medicine to augment the antidepressant effects of tricyclic antidepressants and selective serotonin reuptake inhibitors. Its antidepressant effects occur quickly compared with those of tricyclic antidepressants and selective serotonin reuptake inhibitors, and it has a lower potential for drug interactions. It is useful in patients whose condition has failed to respond to classic antidepressant agents.

Specifically, methylphenidate is used in palliative medicine to improve opioid analgesia and reduce sedation. It also improves cognition in patients with brain tumors without inducing seizures and allows for steroid dose reduction, which is a major benefit. It may also work in leukoencephalopathy resulting from central nervous system radiation.

Ketorolac to enhance opiate analgesia

Ketorolac, a parenteral nonsteroidal anti-inflammatory drug, is used in palliative medicine as an adjuvant to opiate analgesia. Patients with advanced intraabdominal carcinoma who receive opioids for pain are at risk for partial or complete bowel obstruction or opiate bowel syndrome. The tendency is to give more opioids to treat the pain of cramps, but this exacerbates the obstruction. Ketorolac can relieve the pain without contributing to bowel obstruction. It can be given via continuous or subcutaneous infusion (intramuscular or intravenous).

TREATMENTS FOR GASTROINTESTINAL PROBLEMS

Glycopyrrolate for bowel obstruction

Glycopyrrolate is an anticholinergic drug used as an antisialagogue in children with neuromuscular and obstructive esophageal disorders. Its niche in palliative care is as an effective treatment of bowel obstruction. It is used by itself or as part of a three-drug regimen with morphine and haloperidol. Glycopyrrolate has few cardiac effects and can be given subcutaneously, orally, and intravenously.

Nitroglycerin for dysphagia, odontophagia, rectal fissures

Nitroglycerin (glycerin trinitrate), long a standard in the treatment of angina, congestive heart failure, and pulmonary hypertension, has become useful in the palliation of motor dysphagia and odontophagia in patients with advanced cancer when other therapies fail. In addition, it effectively reduces pain and accelerates healing of rectal fissures when applied as a dilute ointment.

Baclofen for hiccups

Baclofen, normally used to treat reversible spasticity associated with multiple sclerosis, has become the preferred treatment for refractory hiccups in palliative care. In patients with gastric distension, esophageal disorders, diaphragmatic irritation, or bone metastases, or who are short of breath, hiccups can be devastating. The first choice for treatment should be an over-the-counter oral antacid. But when that fails, we find that the problem often responds to baclofen.

ONDANSETRON FOR NAUSEA, VOMITING, PRURITUS

Ondansetron is a 5-HT3 antagonist used to treat intractable nausea and vomiting associated with advanced cancer or acquired immune deficiency syndrome. The response rates are as high as 80% among patients not helped by standard antiemetics. Ondansetron also controls nausea and vomiting associated with spinal opioid therapy.

An off-label use of ondansetron is for the treatment of pruritus in patients with uremia or hepatic disease. In these patients, pruritus is thought to be related to serotonin release rather than histamine release. Ondansetron reduces serotonin levels and relieves pruritus within 2 weeks.

PAROXETINE FOR PRURITUS

Paroxetine is a selective serotonin reuptake inhibitor known for its antidepressant qualities. Its use in palliative medicine to relieve pruritus in patients with advanced cancer may seem paradoxical: one would think that inhibiting serotonin reuptake would worsen the condition. But prolonged paroxetine therapy actually down-regulates postsynaptic serotonin receptors and reduces serotonin release, eventually relieving pruritus.

VENLAFAXINE FOR HOT FLASHES

Venlafaxine, an antidepressant that inhibits neuronal serotonin and norepinephrine uptake, is used in palliative medicine as a nonhormone treatment of hot flashes in patients undergoing hormone deprivation therapy for advanced prostate cancer or breast cancer. Half of patients with hot flashes associated with hormone manipulation experienced relief with low doses of venlafaxine. The starting dosage is 12.5 mg twice daily and is increased as needed.

THALIDOMIDE FOR ANOREXIA AND CACHEXIA

Anorexia and cachexia are very common in patients with advanced cancer, and interest in thalidomide as a treatment is on the rise. Thalidomide is mildly antianxiolytic and antiemetic and is purported to have antiangiogenic and antitumor effects, as well. A recent study found that low-dose thalidomide (100 mg per night) reduced restlessness and nausea and improved appetite, sleep, and subjective well-being to a degree equal to that produced by megestrol acetate.

Ondansetron and paroxetine are also used to treat pruritus

SUGGESTED READING

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CME ANSWERS

Answers to the credit test on page 599 of this issue

1 **E** 2 **A** 3 **C** 4 **C** 5 **C** 6 **D** 7 **E** 8 **A** 9 **A** 10 **B**
11 **A** 12 **D** 13 **A** 14 **A**