

Guideline for the Treatment of Opioid Neurotoxicity

Definition

Patients on chronic opioids can develop neuroexcitatory side effects: hyperalgesia (increased sensitivity to pain), cognitive changes (disordered attention and impaired short-term memory), delirium with hallucinations, myoclonus.

Etiology

This can be due to an opioid dose which is too high for the patient, dehydration and/or renal failure.

General Approach

Review the medical record (pattern of opioid use and dose escalation, other medications, the presence of electrolyte abnormalities and major organ dysfunction). Whenever medically appropriate, easily treatable causes or exacerbating factors should be corrected (e.g., correct hypomagnesemia).

Treatment Strategies

1. **Opioid dose reduction.** Make sure you are not reducing the opioid dose solely to control side effects at the expense of good pain control. Consider changing the frequency if renal function is impaired (i.e., from q4h to q6h)
2. **Rotate to a dissimilar opioid.** Rotating to a lower dosage of a structurally dissimilar opioid will often reduce neuroexcitatory effects within 24 – 48 hours, while achieving comparable pain control. Rotation is especially important in patients with opioid-induced hyperalgesia. Decrease the morphine equianalgesic dose by 25 – 50% when switching to a new opioid (to account for incomplete cross tolerance). Use immediate release formulations until a new stable dose is achieved.

To rotate a patient to a new opioid, use the following equianalgesic ratios (see chart on page 3):

Oral Routes:

Morphine 10 mg = Oxycodone 5 mg = Codeine 100 mg = Hydromorphone 2 mg

Oral to Subcutaneous Routes:

Ratio (PO) 2:1 (IV/SC)

i.e., Morphine 10mg PO = Morphine 5mg IV/subcut

or Hydromorphone 10mg PO = Hydromorphone 5mg IV/subcut

Transdermal Fentanyl/ Fentanyl infusion:

There are various accepted methods. Easiest method is use the ratio:

Morphine 10 mg IV/SC (or equivalent) per 24 hours = Fentanyl 100 mcg IV/SC per 24 hours

- A patient who used 25mg of Morphine IV/SC in 24 hours would require 250mcg of Fentanyl IV/SC in 24 hours \approx 10mcg/hr infusion or transdermal patch¹ as a starting dose

Supportive Care

1. Encourage oral, IV or subcutaneous hydration to improve elimination of previous opioid metabolites
2. Consider adding a neuroleptic (i.e., haloperidol) for severe symptoms of agitation/delirium
3. Tell the family that this will take 24-48 hours before they see an improvement in symptoms

Rotation example:

A patient is admitted with some delirium and dehydration. She is currently on morphine sustained release 60mg q12h with morphine immediate release 10mg q1h prn. In the past 48 hours, she has taken 3 prn's per day on average. She is presumed to be neurotoxic from the morphine. While awaiting some results regarding other potential causes of her delirium, an opioid rotation is recommended.

⇒ Calculate total daily morphine oral equivalent:

$$120\text{mg (sustained release)} + 30\text{mg (total breakthroughs per day)} = 150\text{mg per day}$$

⇒ Convert to hydromorphone oral: (hydromorphone is 5x stronger than morphine)

$$\frac{150\text{mg}}{n} = \frac{10}{2} \quad n = 30\text{mg hydromorphone PO in 24 hours}$$

or

$$150\text{mg} \div 5 = 30\text{mg hydromorphone PO in 24 hours}$$

⇒ Decrease dose by 25%: (to account for incomplete cross tolerance)

$$30\text{mg} \times 0.75 = 22.5\text{mg hydromorphone PO in 24 hours}$$

⇒ Because she is not reliably swallowing, decision make to change to subcutaneous route: (parenteral is twice as strong as oral)

$$22.5\text{mg} \div 2 = 11.25\text{mg hydromorphone SC in 24 hours}$$

⇒ Divide into doses for q4h dosing: (consider q6h dosing if renal failure or frail elderly)

$$11.25\text{mg} \div 6 \text{ doses in 24 hours} = 1.875\text{mg per dose}$$

\approx 2mg hydromorphone subcut q4h

⇒ Ensure breakthrough is ordered (10% of daily dose)

$$11.25\text{mg} \times 10\% = 1.125\text{mg}$$

\approx 1mg hydromorphone subcut q1h PRN

¹ Note a fentanyl patch takes 12 hours to reach peak effectiveness so the previous opioid should be continued for 12 hours, ideally a fentanyl infusion is used initially for easier dose titration.

Opioid Equianalgesic Dose Conversion Table
– equivalence to 10mg Morphine PO

Drug	PO Dose	PO:SC Ratio	SC Dose
Morphine	10 mg	2:1	5 mg
Codeine	100 mg	2:1	50 mg
Tramadol	100 mg		
Oxycodone	5 – 7.5 mg		
Hydromorphone	2 mg	2:1	1 mg
Fentanyl infusion/patch (based on 24 hour dose, can be variable)			2 – 5 mcg/hr

Adapted from The Pallium Palliative Pocketbook 2nd edition, 2018