GUIDELINES FOR THE NEUROPATHIC PAIN MANAGEMENT

Benítez-Rosario MA, Doyle R, M^{c}Darby G, Hanningan M
Galway Hospice Foundation, 2007
Ireland

GUIDELINES (I)

<table>
<tr><th>Patient Condition</th><th>ACTION - TREATMENT</th></tr>
<tr><td>In all patients</td><td>Dexamethasone,8-16 mg/d, and radiotherapy treatment should be considered if nerve compression is suspected</td></tr>
<tr><td>Opioid-naïve patients</td><td>Start Opioid treatment

SR-morphine (or oxycodone) plus NR- morphine q1h p.r.n (or oxycodone or OTF) in Mild-Moderate pain
&
CSCI / CIVI plus rescue doses of morphine q30 min p.r.n in Severe Pain
…….
Upward dose titration of the opioid (increasing 30-50% of prior daily dose not including rescue dose administered until: (i) pain relief , (ii) unacceptable side effects occur, (iii) clinical condition of partial response to usual oral opioid dose</td></tr>
<tr><td>Patients who are on opioid treatment AND neurotoxicity effects occur</td><td>Switch to other opioid on equivalent doses</td></tr>
<tr><td>Patient with partial response to usual oral opioid doses and no side effects

(see additional information)</td><td>Considerer this situation when pain is not improving ≥ 50% in spite of

<table><tr><td>a) Slow increase of oral opioid, or equivalent parenteral doses, up to</td><td>Morphine: 260 mg/d
Oxycodone: 130 mg/d
Hydromorphone 50 mg/d
Transdermal Fentanyl 125 mcg/h</td></tr><tr><td>b) Rapid escalation of opioid oral dose, or equivalent parenteral doses, in the last 10 days, up to</td><td>Morphine: 180mg/d
Oxycodone: 90 mg/d
Hydromorphone 30 mg/d</td></tr></table>
ACTION
Rule out other complications
(delirium, psychological problems, non-treatment compliance)

Select one option
a) Leave same doses of opioids and start a co-analgesic
b) Increase daily opoid dose, by 50%, and start a co-analgesic drug.
c) Consider invasive treatments, e.g. nerve block
d) Consider Ketamine treatment in patients who are in severe pain</td></tr>
<tr><td>Patient with partial response to opioid treatment plus maximal doses of one co-analgesic and no opioid side effects

(see additional information)</td><td>Rule out other complications
(delirium, psychological problems, non-treatment compliance)

Select one option
a) Consider increasing opoid doses, and start a second co-analgesic drugs
b) Consider increasing opoid doses and switch to other co-analgesic drugs if the first was completely ineffective (pain relief < 50%)
c)Consider invasive treatment, eg nerve block or intraspinal analgesia
d) Ketamine treatment should be considered in patients who are in severe pain</td></tr>
<tr><td>Patient with partial response to opioids and short-term prognosis</td><td>Start Ketamine treatment</td></tr>
</table>

SR: sustained release; NR: normal release; CSCI: continuous subcutaneous infusion, CIVI: continuous intravenous infusion; p.r.n: as needed; OTF: oral transmucosal fentanyl, q1h:every hour; q30 min: every 30 minutes

GUIDELINES (II): CO-ANALGESIC SELECTION

<table>
<tr><th>Patient Condition</th><th>Treatment</th></tr>
<tr><td>a) If the patient has coexisting anxiety or depression</td><td>
<table>
<tr><td></td><td>Amitriptyline & Nortriptyline
Starting dose 25 mg / d
After 2-3 days increase up to 50 mg/d
Increase weekly 25 mg/d up to 100 mg/d
Usual effective dose: 50-150 mg/d

Venlafaxine
Starting dose 37.5-75 mg /d
Usual effective dose: 75-150 mg/d</td></tr>
<tr><td>Old & Frail patients
……
Cardiac illness & Glaucoma</td><td>Duloxetine
Starting doses 30 mg/d.
After 2-3 days, increase up to 60 mg/d
Usual effective dose: 60 mg/d</td></tr>
</table>
Amitriptyline could be used:
a) in older patients increase 10 mg every 3 – 4 days to avoid strong side effects
b) in patients with insomnia use above schedule
c) fisrt line in all patients & second line when other co-analgesics fail.

Amitriptyline, Nortriptyline, Venalfaxine and Duloxetine should be started with opioids in depressed patients who experience neuropathic pain</td></tr>
<tr><td>b) If the patient has NO coexisting insomnia, anxiety or depression</td><td>……

Selecting Gabapetin or Pregabalin
<table>
<tr><td>Gabapentin</td><td>Starting dose 400 mg/d.
Increase by 300 mg/d up to 1200 mg/d.
Increase weekly 400-600 mg /d
Usual Effective dose: 900-5400 mg/d</td></tr>
<tr><td>Pregabalin</td><td>Starting dose 75-150 mg/d
Increase weekly 150 mg/d
Usual Effective dose:150 -300- 600 mg/d</td></tr>
</table></td></tr>
<tr><td>c)Patients unable to take oral tablets</td><td>……

Selecting Oxcarbazepine (when Gabapentin solution is not available)
Starting dose: 75-150mg/d
Increase weekly 150 mg/d
Usual effective dose: 300-1200 mg/d
……</td></tr>
<tr><td>d) Patients with short-term prognosis or patients in severe pain</td><td>Ketamine
CSCI of 0.1 mg /kg /h
Increase by 0.05-0.1 mg/kg/h every day
Usual effective dose: 0.1-0.3 mg/kg/h

Administer Haloperidol 3 mg /24 h (in the same CSCI) or diazepam 5 mg/d p.o. or Midazolam 5-7.5 mg/24 h CSCI, to control side effects</td></tr>
</table>

ADITIONAL INFORMATION

- Latest evidence shows that the opioids are equal, or more effective than co-anagelsics to relieve neuropathic pain
- Opioids relieve pain quicker, in 24-72 h, than co-analgesics. The co-analgesics need, at least, 7-10 days to improve pain.
- The greater benefits from quicker relief of neuropathic pain with opioids counteracts the side effect risks. Some protocols establish upward dose titration of opioids until pain relief or side effects occur
- Available data indicates no difference in analgesic efficacy of different opioids in neuropathic pain and there is also no significant difference in the efficacy of co-analgesics. Tricyclic Antidepressants, Gabapentine, Pregabaline, Venlafaxine, Duloxetin and Oxcarbazepine are equally effective.
- Co-anagelsic selection should be according to patients condition (e*g* depressed / not depressed), side effect profile and cost
- Opioid dose should be reduced, by 30-50%, when a co-analgesic has been started and patient is pain free. Consider this situation with ketamine treatment as well.
- Depression in cancer patients can respond to lower doses of antidepressants than the general population

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