Pain control: How can we optimize the pain medication for HCC patients?

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Chonnam National University Medical School
### Symptoms and Prevalence

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prevalence n (%)</th>
<th>Severity* Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling fatigued</td>
<td>189 (97.42)</td>
<td>5.03 ± 2.59</td>
</tr>
<tr>
<td>2. Lack of energy</td>
<td>171 (88.14)</td>
<td>4.79 ± 2.69</td>
</tr>
<tr>
<td>3. Stomach pain/discomfort</td>
<td>140 (72.16)</td>
<td>4.23 ± 2.55</td>
</tr>
<tr>
<td>4. Loss of appetite</td>
<td>131 (67.53)</td>
<td>4.15 ± 2.75</td>
</tr>
<tr>
<td>5. Change in taste</td>
<td>131 (67.53)</td>
<td>4.30 ± 2.70</td>
</tr>
<tr>
<td>6. Indigestion</td>
<td>130 (67.01)</td>
<td>4.03 ± 2.57</td>
</tr>
<tr>
<td>7. Itching</td>
<td>129 (66.49)</td>
<td>3.89 ± 2.53</td>
</tr>
<tr>
<td>8. Feeling ill</td>
<td>129 (66.49)</td>
<td>3.53 ± 2.23</td>
</tr>
<tr>
<td>9. Sadness</td>
<td>126 (64.95)</td>
<td>4.46 ± 2.71</td>
</tr>
<tr>
<td>10. Pain</td>
<td>117 (60.31)</td>
<td>4.10 ± 2.81</td>
</tr>
<tr>
<td>11. Nausea</td>
<td>114 (58.76)</td>
<td>4.18 ± 2.59</td>
</tr>
<tr>
<td>12. Weight loss</td>
<td>111 (57.22)</td>
<td>3.71 ± 2.76</td>
</tr>
<tr>
<td>13. Back pain</td>
<td>103 (53.09)</td>
<td>3.76 ± 2.56</td>
</tr>
<tr>
<td>14. Spending all day in bed</td>
<td>100 (51.55)</td>
<td>3.59 ± 2.24</td>
</tr>
<tr>
<td>15. Diarrhea</td>
<td>95 (48.97)</td>
<td>3.52 ± 2.66</td>
</tr>
<tr>
<td>16. Constipation</td>
<td>94 (48.45)</td>
<td>3.83 ± 2.52</td>
</tr>
<tr>
<td>17. FEVERS</td>
<td>87 (44.85)</td>
<td>3.58 ± 2.71</td>
</tr>
<tr>
<td>18. Side effects</td>
<td>82 (42.27)</td>
<td>4.03 ± 2.64</td>
</tr>
<tr>
<td>19. Jaundice</td>
<td>74 (38.14)</td>
<td>3.83 ± 2.60</td>
</tr>
<tr>
<td>20. Stomach swelling/cramps</td>
<td>62 (31.96)</td>
<td>3.02 ± 2.41</td>
</tr>
</tbody>
</table>

*MS Cho, J Korean Acad Nurs. 2009*
HCC pain I: cancer related pain

Cancer related pain

- Glisson’s capsule invasion
- Volume expansion
- Referred pain
- HCC rupture

Metastatic pain

- Long term pain
- Etiology based treatment

Etiology based treatment: Important to drug choice
HCC pain II: Treatment related pain

Treatment related Pain

- TACE or RFA
- Radiation
- Chemotherapy

: Inflammation

: Short term

: Repetitive

: Need to monitoring for secondary complication
HCC pain III: Underlying disease

Other pain

Underlying disease

: Differential diagnosis
Consultation
통증 평가

통증조사

• PQRST

• 위치 (Position)
• 양상 (Quality)
• 관련된 인자 (Relieving or aggravating factor)
• 통증 강도 (Severity)
• 시간 (Time)

통증 및 통증 조절에 대한 잘못된 믿음 여부 조사

암성통증관리지침 권고안 5판
54/M
Infiltrative HCC with PVT
Child A
HAIC
Complain to RUQ pain
Missing symptom evaluation
After HAIC 2 cycle: active duodenal ulcer
Dead by ulcer bleeding
2 month later
- **Numeric Rating Scale, NRS**

  - 숫자 등급 (Numeric Rating Scale, NRS)

  ![Numeric Rating Scale](image)

- **Faces Pain Rating Scales**

  - 얼굴 통증 등급 (Faces Pain Rating Scales)

  ![Faces Pain Rating Scales](image)
Choice of Analgesics

Old Guideline (WHO)

- Non-Opioids
- Weak Opioids
- Strong Opioids

Ladder concept

New Guideline (NCCN)

- Pain Intensity 1~3: Non-Opioid
- Pain Intensity 4~10: Opioid

Pain intensity concept

NCCN guideline 2012
Pain control in HCC patient

- **Pain assessment** – Relation to disease

- **Pain intensity** - Choice of analgesics: opioid or non-opioid

- **Pain duration** – Consider drug complication: Dose calculation

- **Pain characteristics** – Norciceptive pain or neuropathic pain

+ Liver function
Drug metabolism in liver dysfunction

Impair drug metabolism
• cytochrome P450 system
• conjugation
• biliary excretion

Low serum albumin (binding protein)
• Increased level of free drug

Impair renal function
• normal Cr level
• less creatinine production
• malnutrition, reduced muscle volume

Decreased portal blood flow

Increased drug level and bioavailability

adverse events

Elbekai R. Eur J Cli Pharmacol 2004
Adverse events of analgesics in liver cirrhosis

Conventional adverse event

- Opioids
  - Constipation
  - Nausea and vomiting
  - Sedation
  - Respiratory depression
  - Addiction and dependency

- Non-opioids
  - Hepatotoxicity
  - Peptic ulcer
  - Renal impairment

Adverse event in liver disease

Opioids

- Hepatic encephalopathy
- Sedation
- Delirum

Non-opioids

- Hepatotoxin – liver dysfunction
- Renal impairment - hepatorenal syndrome
- GI bleeding
Non-opoid analgesics
Chronic alcoholics, malnutrition, liver disease – risk factor

- cytochrome P450
- Depletion of glutathione
Acetaminophen

- **Dose dependent direct hepatotoxin**
  - Possible liver injury: single dose of 10-15g
  - Fulminant hepatitis ≥ 25 g (usually)
  - Most common cause of acute hepatic failure

- In 20 patients with chronic liver disease, AAP 4g/d for 13 days – no adverse event
  
  Benson GD, Clin pharamcol Ther 1983

- Short-term use: tolerable to 3-4 g/day

- FDA guideline recommend
  - **Maximal dose (2 to 3g/day) in chronic liver disease**

  Benson GD, Am J Ther 2005
- Idiosyncratic hepatotoxin
- Renal impairment (inhibition of prostaglandin) leading to hepatorenal syndrome
- GI bleeding including variceal and non-variceal bleeding
  - 4876 cirrhosis pt (NASID)
  - Cox 2 inhibitor (OR= 1.44, 95% CI 0.89-2.31)
  - Oral NSAID (OR=1.87, 95% CI 1.66-2.11)
  - IV NSAID (OR=1.90, 95% CI=1.55-2.32)
  - NASID + PPI or H2 blocker : lower GI bleeding

- Cox-2 inhibitor – low GI bleeding, high cardiovascular event
  - Safety is not confirm in cirrhosis

- Avoid to long term use

Lee YC, Liver Int 2012
## Opioids

- **Morphine**
- **Hydromorphone**
- **Oxycodone**
- **Fentanyl**
- **Codein**
- **Tramadol**
- **Hydrocodone**
- **Levorphanol**
- **Methadone**
- **Meperidine**

<table>
<thead>
<tr>
<th>약품명</th>
<th>투여간격</th>
<th>제형</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>4~6시간</td>
<td>인신 코드인정 26mg, 대표인정 20mg</td>
</tr>
<tr>
<td>Codeine 10mg + Ibuprofen 200mg + paracetamol 250mg</td>
<td>8시간</td>
<td>마이플 캡슐, 씨아이에이 캡슐, 마이프로필 캡슐, 코노론 캡슐, 터코판 캡슐</td>
</tr>
<tr>
<td>Hydrocodone 60mg</td>
<td>12시간</td>
<td>다크테 서방정</td>
</tr>
<tr>
<td>Tramadol 50mg</td>
<td>4~6시간</td>
<td>토론론캡슐</td>
</tr>
<tr>
<td>Tramadol 100mg</td>
<td>12시간</td>
<td>토론론캡슐, 지징서방정, 지판서방정</td>
</tr>
<tr>
<td>Tramadol 150mg</td>
<td>24시간</td>
<td>토론론캡슐, 지징서방정, 코트럼 영업원 서방정</td>
</tr>
<tr>
<td>Tramadol 200mg</td>
<td>24시간</td>
<td>지징서방정</td>
</tr>
<tr>
<td>Tramadol 주사제</td>
<td></td>
<td>Tramadol HCL주</td>
</tr>
<tr>
<td>Tramadol + Acetaminophen</td>
<td>6시간 이상</td>
<td>올트라셋 세이 정 18.75/162.5mg, 올트라셋 정 37.5/325mg</td>
</tr>
<tr>
<td>Morphin 주사제</td>
<td>12시간</td>
<td>올트라셋 이열 정 75/650mg</td>
</tr>
<tr>
<td>Morphin (속착성) 15mg</td>
<td>2~3시간</td>
<td>황열판정, 에스플판정</td>
</tr>
<tr>
<td>Morphin (서방정) 10mg</td>
<td>12시간</td>
<td>염페시스서방정, 염페시스서방정</td>
</tr>
<tr>
<td>Morphin (서방정) 30mg</td>
<td>12시간</td>
<td>염페시스서방정</td>
</tr>
<tr>
<td>Oxycodone (속착성) 5mg</td>
<td>4~6시간</td>
<td>0이알복정, 오코돈, 염페다음</td>
</tr>
<tr>
<td>Oxycodone (서방정)</td>
<td>12시간</td>
<td>염페시스서방정 10mg, 20mg, 40mg, 80mg</td>
</tr>
<tr>
<td>Oxycodone (서방정) + Naloxone</td>
<td>12시간</td>
<td>타진 서방정 10/5, 20/10mg</td>
</tr>
<tr>
<td>Oxycodone + Acetaminophen</td>
<td>6시간</td>
<td>타이레놀옥시캡슐 5/500mg</td>
</tr>
<tr>
<td>Fentanyl 캡슐</td>
<td>72시간</td>
<td>드로제식트랜스페치 12mcg/hr, 25mcg/hr, 50mcg/hr, 100mcg/hr, 펜터스 페치 25mcg/hr, 50mcg/hr, 펜터스 MAT페치 12.5mcg/hr, 25mcg/hr, 50mcg/hr, 100mcg/hr</td>
</tr>
<tr>
<td>Fentanyl [구강 penet] 15분</td>
<td>최소 15분</td>
<td>액체정 200/400/600/800/1200/1600mcg</td>
</tr>
<tr>
<td>Hydromorphone (서방정)</td>
<td>24시간</td>
<td>저니스타 서방정 4mg, 8mg, 16mg, 32mg, 64mg</td>
</tr>
<tr>
<td>Hydromorphone (속착성)</td>
<td>4~6시간</td>
<td>저니스타 이글 2mg, 딜리트 정 2mg, 4mg</td>
</tr>
<tr>
<td>Hydrocodone + Acetaminophen</td>
<td>4~6시간</td>
<td>허리코돈정 5mg(hydrocodone 5mg/acetaminophen 500mg), 7.5mg (hydrocodone 7.5mg/acetaminophen 500mg)</td>
</tr>
</tbody>
</table>

* KIMS online 2012.5.3 기준*
Opium-poppy (*Papaver somniferum*)
History of opioids

Opium derivative alkaloids
- Morphine, 1804 German
- Codein, 1832, France

Semi-synthetic opioids
- Hydromorphone, 1924 German
- Oxycodone, 1916 German

Synthetic opioids
- Meperdine, 1932 German
- Fentanyl, 1959 Janssen Pharm
- Tramadol, 1977
Opioids: Acting Time

“Short-acting”
- Morphine S-morphine®
- Hydromorphone
- Codeine
- Hydrocodone
- Oxycodone IR codon®
- Fentanyl Actiq®
- Meperidine

“Ultra-short acting”
- IV, SC, Transmucosal

“Long-acting”
- Extended release morphine
  - MS Contin®
- Oxycodone ER
  - Oxycontin®, Targin®
- Hydromorphone OROS®
  - Jurnista®
- Transdermal fentanyl
  - Durogesic® (Matrix)
  - Fentas® (Reservoir)
General principle of opioid in cancer

- No ceiling effect

- Route
  - Oral (m/c), IV, SC, transdermal, rectal, transmucosal…

- Dose calculation
  - Total opioid dose taken in previous 24hr

- Pure opioid
  - Insufficient response of combined drug (opioid + NSAID) : switch to pure opioids (avoiding toxicity of NSAID)

NCCN guideline 2012
Opioid rotation

- Combination of two opioids – Increasing adverse event: Not recommend
- If pain was uncontrolled or adverse event
  - Increasing dose
  - Change to another opioid: Opioid rotation

<table>
<thead>
<tr>
<th>종류</th>
<th>총 투여 환자수</th>
<th>이상반응 응답 환자</th>
<th>발현 환자</th>
<th>발현 비율(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-TRANS only</td>
<td>441</td>
<td>415</td>
<td>107</td>
<td>25.8</td>
</tr>
<tr>
<td>SR morphine only</td>
<td>93</td>
<td>82</td>
<td>16</td>
<td>19.5</td>
</tr>
<tr>
<td>CR oxycodone only</td>
<td>325</td>
<td>313</td>
<td>84</td>
<td>26.8</td>
</tr>
<tr>
<td>IV morphine only</td>
<td>68</td>
<td>56</td>
<td>19</td>
<td>33.9</td>
</tr>
<tr>
<td>D-TRANS + CR oxycodone</td>
<td>194</td>
<td>179</td>
<td>79</td>
<td>44.1</td>
</tr>
<tr>
<td>D-TRANS + SR morphine</td>
<td>33</td>
<td>25</td>
<td>11</td>
<td>44.0</td>
</tr>
<tr>
<td>D-TRANS + morphine (I.V)</td>
<td>37</td>
<td>28</td>
<td>11</td>
<td>39.3</td>
</tr>
<tr>
<td>CR Oxycodone + SR morphine</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CR Oxycodone + morphine (I.V)</td>
<td>10</td>
<td>9</td>
<td>2</td>
<td>22.2</td>
</tr>
<tr>
<td>SR Morphine + morphine (I.V)</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>50.0</td>
</tr>
</tbody>
</table>

26.1%
41.8%
Choice of opioids in cirrhosis?

- Use of short period (below 2 week) : any drug
- Use of long period : **Hydromorphone, Fentanyl, Tramadol**

- Stable drug level
  - Active form without hepatic metabolism
  - Less transporter protein (albumin) binding
- Less toxicity
  - Liver, Kidney, CNS
- Less sedation and hemodynamic disturbance
- Less constipation

Natasha C. Mayo Clin Proc 2010
<table>
<thead>
<tr>
<th>Drug</th>
<th>Half life (h)</th>
<th>Protein binding (%)</th>
<th>Hepatic metabolism</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>1-3</td>
<td>15</td>
<td>Glucuronidation</td>
<td>No renal toxicity</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1-3</td>
<td>80</td>
<td>CYP3A4</td>
<td>Less hemodynamic disturbance</td>
</tr>
<tr>
<td>Morphine</td>
<td>3-12</td>
<td>35</td>
<td>Glucuronidation</td>
<td>Renal toxicity</td>
</tr>
<tr>
<td>Codein</td>
<td>4-6</td>
<td>7</td>
<td>CYP2D6</td>
<td>Metabolized to morphine in liver</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2-12</td>
<td>45</td>
<td>CYP3A4, 2D6</td>
<td>Metabolized to Hydromorphone and oxymorphone in liver, levels unpredictable</td>
</tr>
<tr>
<td>Tramadol</td>
<td>7</td>
<td>20</td>
<td>CYP3A4, 2D6, glucuronidation</td>
<td>Anticholinergic effect</td>
</tr>
<tr>
<td>Meperidine</td>
<td>8-24</td>
<td>70</td>
<td>CYP3A4, 2D6</td>
<td>Normeperidine – CNS toxicity</td>
</tr>
</tbody>
</table>
Increased CNS sensitivity of opioid agonist

- Up regulation of central mu-opioid receptor in cirrhosis with encephalopathy
- HE stage II, III, IV: 15, 29, 33% of density of brain mu receptor

Increased drug level and half life

- Morphine: double half life in cirrhosis patient (3-12 hr vs 3-6 hr in normal patient)

Constipation
Weak opioid agonist
Mainly effect to peripheral pain pathway more than brain
Partial inhibition of serotonin reuptake

Advantage: less sedation, respiratory depression
Disadvantage

• Anticholinergic adverse event (constipation)
• Serotonin syndrome - Should not be combined to other drug (morphine, SSRI, tricyclic antidepressant, anticonvulant…)

Ex) Ultracet® (tramadol + acetaminophen) + morphine..

Kotb HI, J Opioid Manag. 2008
Consider 2\textsuperscript{nd} choice
Oral opioid vs transdermal patch: no inferiority

- Advantage compared with oral opioid
  - Less hemodynamic disturbance
  - Less sedation and constipation
  - Less day drowsiness

- High cost
- Child swallowing accident
Short acting fentanyl: Actiq®

Oral Transmucosal Fentanyl Citrate

Benefits

Rapid onset of action
Controllable dose-to-effect
Improved safety
Convenience
Non-invasive, non-threatening
Method of Actiq®

1. Remove the safety cover.
2. Place the Actiq® lozenge on the tongue.
3. Let it dissolve for 15 minutes.

(Imagery of a person holding the Actiq® package, putting it on the tongue, and the timer showing 15 minutes.)
Hydromorphone

Data on file, ALZA Corporation.
- New oral prolonged release formulation
- Dose ratio of 2:1 oxycodone to naloxone
• Metabolite (normeperdine) : CNS toxicity
• Increased bioavailability (heavy protein binding) and prolong half life in liver disease
• Contraindication to cancer pain control (long term use)
INITIATING SHORT-ACTING OPIOIDS IN OPIOID NAIVE PATIENTS

Monitor for acute and chronic adverse effects. (See Management of Opioid Adverse Effects PAIN-F)

Opioid naïve patients

<table>
<thead>
<tr>
<th>Initial Dose</th>
<th>Subsequent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (peak effect 60 min)</td>
<td>After 2-3 cycles, consider IV titration and/or see PAIN-6 for subsequent management and treatment</td>
</tr>
<tr>
<td>Dose 5-15 mg oral short-acting morphine sulfate or equivalent (See PAIN-E)</td>
<td>Increase dose by 50-100%</td>
</tr>
<tr>
<td>Reassess efficacy and adverse effects at 60 min</td>
<td>Pain score decreased to 4-6</td>
</tr>
<tr>
<td>Pain score unchanged or increased</td>
<td>Repeat same dose</td>
</tr>
<tr>
<td>Pain score decreased to 0-3</td>
<td>Continue at current effective dose as needed over initial 24 h</td>
</tr>
</tbody>
</table>

Pain ≥ 4
See Pain Intensity Rating (PAIN-A) or As indicated for uncontrolled pain (patient goals not met)

Intravenous bolus (peak effect 15 min) or patient-controlled analgesia

Dose 2.5 mg intravenous morphine sulfate or equivalent (See PAIN-E)

Reassess efficacy and adverse effects at 15 min

Pain score unchanged or increased

Increase dose by 50-100%

Pain score decreased to 4-6

Repeat same dose

Pain score decreased to 0-3

Continue at current effective dose as needed over initial 24 h

See Subsequent Pain Management - Mild Pain 0-3 (PAIN-6)

After 2-3 cycles, see PAIN-6 for subsequent management and treatment

Opioid naïve includes patients who are not chronically receiving opioid analgesics on a daily basis.

Subcutaneous can be substituted for intravenous, however peak effect subcutaneously is usually 30 min.
Overview in opioid use in cancer

1. Dose calculation by short acting opioid

2. Decision of dosage of long acting opioid

3. Maintain to long acting opioid + prn med (short acting opioid, 10-20% of total dose)
암성통증관리지침 권고안

Dose calculation

통증 4~6 또는 7~10

속효성 경구용 모르핀†

처음 사용자

사용 중인 자

속효성 경구용 모르핀† 5~15mg

이전 24시간 총 사용량의 10~20%을 투여

주사용 모르핀

처음 사용자

사용 중인 자

주사용 모르핀 1~5mg

이전 24시간 총 사용량의 10~20%을 투여

60분 후에 통증과 부작용을 재평가

4~6점으로 감소

0~3점으로 감소

통증이 변하지 않거나 심해짐

같은 용량으로 반복

2~3시간 후 재평가

용량을 2배로 늘림

15분 후에 통증과 부작용을 재평가

4~6점으로 감소

0~3점으로 감소

통증이 변하지 않거나 심해짐

같은 용량으로 반복

2~3시간 후 재평가

용량을 2배로 늘림

* NRS(numeric)
† 속효성 경구용 경구용 oxycodone
‡ 통증발생양호 척조
§ 투입 통증에 대하여 속효성 저제 (이전 24시간 총 용량의 10~20%)를 함께 처방

*접수는 NRS(numeric rating scale)로 신청 / 환자의 상태에 따라서 마약성 진통제는 어느 단계에서나 가능하다.
**2~3회 반복 후에도 반응이 없다면 통증 재평가, 특수한 통증 증후군(예: 신경병증통증), 중재적 시술 고려, 보조 진통제 재평가를 고려한다.
1. 속효성 경구 모르핀
규칙 용량 10~20mg q4hr
돌발 통증 5~10mg q1hr prn

2. 서방형 경구 모르핀
30~60mg q12hr

만일 24hr 투여 총 용량이 120mg인 경우

‘정기적인 서방형 모르핀 투여’
60mg q12hr

‘돌발 통증 속효성 모르핀 투여’
이전 24hr 총량의 10~20%를 고려
15mg (12~24mg) q1hr prn

암성통증관리지침 권고안 5판
<table>
<thead>
<tr>
<th>Drug</th>
<th>Morphine 10mg IV</th>
<th>PO: IV</th>
<th>Duration(Hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO</td>
<td>IV/SC</td>
<td></td>
</tr>
<tr>
<td>Morphine®</td>
<td>30</td>
<td>10</td>
<td>1:3</td>
</tr>
<tr>
<td>Codeine®</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jurnista®</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycontin®</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durogesic patch®</td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol®</td>
<td>120</td>
<td>100</td>
<td>1:1.2</td>
</tr>
</tbody>
</table>

Morphine® 30mg = jurnista® 8mg = durogesic patch® 12.5 ug = oxycontin® 20mg

S-morphine® 15mg = actiq® 200mcg
# Pain Diary

"귀하의 통증이 얼마나 심한지를 잘 나타내는 숫자에 표시해 주시거나, 말해 주십시오."

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>통증점수</th>
<th>드로제식패치</th>
<th>양시콘틴</th>
<th>불편 정주</th>
<th>속효성 진통제</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>월 일</th>
<th>월 일</th>
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<th>월 일</th>
<th>월 일</th>
<th>월 일</th>
<th>월 일</th>
</tr>
</thead>
</table>

화순전남대학교병원 혈액중양내과
<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>Time (h)</td>
<td>12</td>
<td>18</td>
<td>0</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (PO) 지속형</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Morphine (PO) 속효성</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Total morphine (24hr)</td>
<td>90</td>
<td>150</td>
<td>210</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Durogesic patch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Neuropathic pain

- **Tricyclic antidepressant**
  - Amitriptyline, imipramine, nortriptyline, desipramine
  - Blocking presynaptic serotonin or noradrenalin reuptake in pain pathway
  - Adverse event is more common in liver disease
    - sedation
    - anticholinergic effect including constipation, dry mouth, drowsiness, orthostatic hypotension

- **Anticonvulsant**
  - Gabapentine, pregabaline (Lyrica®)
  - Correct imbalance of excitatory and inhibitory neurotransmitters
  - Not metabolized by liver, relatively safe in cirrhosis
  - Idiosyncratic hepatotoxin in case report
CASE: Pain = Alarm sign

67/F

Two small HCC
Child B

RFA

Complain to RUQ pain

Pain control – RFA induced pain

After 1 week later
  : Free air
  Delay perforation (hepatic flexure)

1 week later
Pain control in HCC patients

- Decompensated liver function – pain ≥ 4
  - High risk for adverse event (deep sedation)
  - Need to strict dose calculation
    1. Short acting opioid: Oral transmucosal fentanyl (actiq)
    2. Short acting oral opioid
    3. Low dose IV (possibly avoid)

- Transient pain
  - Treatment related pain
  - Monitoring to secondary complication
  - Dosage of analgesics > Kinds of analgesics
  - Pain intensity (1-3: Non-opioid, over 4: Opioid, short acting)
  - Anti-inflammatory drug (AAP, Cox 2 inhibitor)
Pain control in HCC patients

- Sustained pain
  - Cancer related pain
  - Choice of analgesics: Step up (ladder), AAP or Tramadol
  - Avoiding to adverse event: careful choice and dose calculation, f/u
  - Fentanyl patch
Analgesic approach in HCC patients

HCC pain

Visceral or musculoskeletal
- Acetaminophen, <2-3 g/day
- Tramadol

Neuropathic
- Amitriptyline or/and Gabapentine or Pregabalin (Lyrica®) and Acetaminophen, <2-3 g/day

Pain intensity

1-3
- Acetaminophen, <2-3 g/day

≥4
- Tramadol
  - For intractable pain or severe pain, consider Hydromorphone and Fentanyl patch

Do not combine these agents with tramadol
감사합니다！