**Pharmacy Practice: Lecture 5 Dr. Haider Raheem**

**Treatment of Cancer Pain**

**Cancer Pain Etiology**

L.V. is a 58-year-old man who was diagnosed with stage IV squamous cell carcinoma of the subglottis 2 months ago. The cancer is locally advanced with involvement of multiple cervical lymph nodes. He had a modified neck resection to remove the primary tumor and lymph nodes while sparing the larynx. Chemoradiation therapy began 3 weeks after surgery with cisplatin 100 mg/m2 every 3 weeks (days 1, 22, and 43) and external beam radiation delivering 70 Gy fractionated over the course of 7 weeks. L.V. is now in his fourth week of radiation therapy and continues to have significant neck and shoulder pain described as “sudden shocklike sensations with movement” and rated 6 of 10 despite a recent increase in his long-acting oral morphine to 60 mg twice daily with immediate-release morphine 10 mg PO every 4 hours PRN for breakthrough pain. He also reports that his throat is getting so sore that he cannot bear to swallow and rates the pain 10 of 10. L.V. appears quite fatigued and lethargic during his appointment with the radiation oncologist. The physical examination is remarkable for dry oral mucous membranes, erythema and mild ulceration of the oropharynx, and allodynia with light palpitation of the trapezius and sternocleidomastoid with pain greater on the left side. Based on the laboratory tests the radiation oncologist decides to admit L.V. to the hospital for dehydration and pain management. What are the possible etiologies of L.V.’s pain?

L.V. is presenting with a new complaint of a severe sore throat and persistent neck and shoulder pain. Laboratory data rule out infection and myelosuppression. His kidney function may be impaired by dehydration and cisplatin therapy. The most likely causes of L.V.’s pain are the recent surgical neck resection and mucositis from external beam radiation.

L.V. also has postoperative peripheral neuropathy characterized by shocklike sensation in the neck and shoulders after the resection of the tumor.

**Transdermal Fentanyl Dose Calculation**

L.V. was started on IV hydromorphone using patient-controlled analgesia (PCA) with an average usage of 14 mg/day. He now rates his pain as 4 of 10. Owing to difficulty swallowing secondary to the mucositis and xerostomia, he had a gastric feeding tube placed for nutrition. The plan is to convert the IV hydromorphone to a transdermal fentanyl patch. What transdermal fentanyl patch dose should L.V. be started on?

For more than two decades, the World Health Organization’s (WHO) analgesic ladder has been used to guide cancer pain management. The ladder progresses in a stepwise manner starting with acetaminophen, NSAIDs, and adjuvant medications (e.g., coanalgesics such as anticonvulsants and antidepressants for neuropathic pain) as initial therapy. If the pain intensity is greater than 4 of 10 but not severe, weak opioid analgesics may be added to the pain regimen. For severe pain, strong opioids such as morphine, hydromorphone, fentanyl, and oxycodone are recommended in step 3 of the WHO analgesic ladder.

Transdermal fentanyl patches are intended for opioid-tolerant patients with stable chronic pain. Opioid-tolerant patients are those who have been taking daily, for a week or longer, at least 60 mg of oral morphine, 30 mg of oral oxycodone, or at least 8 mg of oral hydromorphone or an equianalgesic dose of another opioid.

Doses of two different opioids (or two different routes of administration of the same opioid) are considered to be equianalgesic if they provide the same degree of pain relief. Table 5-1 gives equianalgesic opioid doses.

**Table 5-1: Equianalgesic opioid doses.**

|  |  |  |
| --- | --- | --- |
| Opioid | Equianalgesic Dose (mg) | |
| Oral | Parenteral |
| Morphine | 30 | 10 |
| Hydromorphone | 7.5 | 1.5 |
| Fentanyl | - | 0.1 |
| Oxycodone | 20 | - |
| Levorphanol | 4 acute  1 chronic | 1 chronic |
| Buprenorphine | 0.3 | 0.4 (sublingual) |
| Meperidine | 300 | 100 |

There are several published tables for converting morphine to transdermal fentanyl (Duragesic®) by researchers and manufacturers of transdermal fentanyl products. They provide slightly different dose conversion recommendations. Duragesic® has wide morphine dose ranges, which may result in underdosing the transdermal fentanyl patch in cancer patients (Table 5-2).

**Table 5-2: Conversion from oral morphine to Duragesic®.**

|  |  |
| --- | --- |
| Oral 24-Hour Morphine (mg/d) | Duragesic Dose (mcg/h) |
| 60–134 | 25 |
| 135–224 | 50 |
| 225–314 | 75 |
| 315–404 | 100 |
| 405–494 | 125 |
| 495–584 | 150 |
| 585–674 | 175 |
| 675–764 | 200 |
| 765–854 | 225 |
| 855–944 | 250 |
| 945–1034 | 275 |
| 1035–1124 | 300 |

Breitbart *et al*. recommend a 2:1 ratio of oral morphine to transdermal fentanyl (i.e., 2 mg oral morphine is equivalent to 1 mcg/hour transdermal fentanyl), resulting in higher transdermal fentanyl doses, which may be excessive for elderly patients. A study by Donner et al. suggested a dose ratio of 60 mg/day oral morphine is equal to 25 mcg/hour transdermal fentanyl, which falls between the manufacturer’s table and the study recommendations by Breitbart *et al*. The Donner conversion ratio is used in most references because it is less likely to cause underdosing or overdosing.

The calculations to convert L.V. from IV hydromorphone to transdermal fentanyl demonstrated in the following steps:

**Step 1:**

Determine the 24-hour total of the opioid that will be converted. For L.V., the 24-hour total of intravenous hydromorphone is 14 mg.

**Step 2:**

Select the equianalgesic dose ratio that corresponds to the opioid and route that will be converted from Table 5-1. Ratio calculations should be set up to correlate the actual dose with the equianalgesic equivalent as shown below:

For conversion of L.V.’s hydromorphone dose, 1.5 mg intravenous hydromorphone is equianalgesic to 30 mg oral morphine:

**Step 3:**

Cross multiply the ratio to determine the total daily dose of oral morphine.

(1.5) (X) = (14) (30)

1.5 X = 420

X = 280 mg of oral morphine

**Step 4:**

Determine L.V.’s transdermal fentanyl patch dose equivalent to 280 mg oral morphine.

*Manufacturer’s Conversion Ratio*

225–314 mg oral morphine/day = 75 mcg/hour transdermal fentanyl

*Donner Study Ratio*

The conversion ratio of 60 mg/day oral morphine to 25 mcg/hour transdermal fentanyl will be used for the calculation.

(60) (X) = (280) (25)

X = 116 mcg/hour transdermal fentanyl

*Breitbart Study Ratio*

The conversion ratio of 2 mg oral morphine to 1 mcg/hour transdermal fentanyl will be used for the calculation.

(2) (X) = (280) (1)

X = 140 mcg/hour transdermal fentanyl

**Methadone Dose Calculation**

L.V. has now completed chemoradiation therapy, and the mucositis pain has resolved. He continues to have persistent burning neuropathic pain rated 8 of 10 in the neck and shoulders and is using transdermal fentanyl 100 mcg/hour along with five doses of immediate-release oral morphine 30 mg per day. He is also taking gabapentin 900 mg orally three times a day and using a Lidoderm patch on each shoulder. L.V.’s oncologist wants to switch to oral methadone for neuropathic pain management. What is the oral methadone dose L.V. should be started on?

Unlike short-acting opioids, methadone has a long half-life that ranges from 15 to 60 hours with a duration of action of 6 to 12 hours. The conversion to methadone is not proportional like other opioid equianalgesic dose calculations. The most commonly used morphine to methadone conversions are given in Table 5-3.

**Table 5-3: Morphine to methadone equianalgesic dose ratio.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Oral Morphine Dose (mg/d) | <100 | 101–300 | 301–600 | 601–800 | 801–1000 | ≥1001 |
| Oral morphine to oral methadone ratio | 3:1 | 5:1 | 10:1 | 12:1 | 15:1 | 20:1 |

The dose of oral morphine falls within the dose range of 301 to 600 mg, which corresponds to a 10:1 oral morphine to oral methadone ratio.

The calculations to convert transdermal fentanyl to oral methadone in L.V. are:

**Step 1:**

Determine the 24-hour total of the opioid that will be converted. For L.V., the transdermal fentanyl 100 mcg/hour patch will need to be converted to oral morphine. In addition, L.V. is using 150 mg/day of immediate-release oral morphine.

*Donner Study Ratio*

The conversion ratio of 60 mg/day oral morphine to 25 mcg/hour transdermal fentanyl will be used for the calculation.

(25) (X) = (100) (60)

X = 240 mg oral morphine

Therefore, the total daily dose of oral morphine is 390 mg (240 mg + 150 mg)

*Breitbart Study Ratio*

The conversion ratio of 2 mg oral morphine to 1 mcg/hour transdermal fentanyl will be used for the calculation.

(1) (X) = (2) (100)

X = 200 mg/day oral morphine

Therefore, the total daily dose of oral morphine is 350 mg (200 mg + 150 mg).

**Step 2:**

Select the equianalgesic dose ratio from the methadone table that corresponds to a total daily morphine use of 390 mg (using the Donner method in step 1).

According to the methadone dose Table 5-3, morphine doses in the range of 301–600 mg correspond to a 10:1 ratio (oral morphine to oral methadone).

(10) (X) = (390) (1)

10X = 390

X = 39 mg of oral methadone/day

If the total daily dose of 350 mg oral morphine is used for the calculation, the total daily dose of methadone would be 35 mg.

**Patient Case**

A patient has metastatic cancer, was on morphine sulphate 60 mg q4h, his physician called the hospital pharmacist asking him about how to convert it to the appropriate daily dose of oxycodone.

30 mg of morphine sulphate = 20 mg of oxycodone

**Answer:**

Morphine 60 mg × 6 = 360 mg/day

Because of tolerance (25 % - 50 %)

So, the actual dose of morphine is 180 mg/day (if we choose 50 % tolerance)

30 mg morphine/180 mg morphine = 20 mg oxycodone/X

X = 120 mg of oxycodone/day

***Homework***

A patient is on morphine I.V. 15 mg q4h. The doctor wants to switch him to SR tablet form. If you know that the equivalent dose of morphine 30 mg is: oxycodone 6 mg, codeine 200 mg, hydromorphone 100 mg; what will be the suitable choice? (hint: consider percent of tolerance = 34 %)

a- 300 mg of codeine q12h

b- 60 mg morphine q12h

c- 15 mg oxycodone q12h

d- 100 mg hydromorphone q12h