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May 2008 "Update on Pain Management" 707-000-08-005-H01-P

PAIN MANAGEMENT

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HAVE YOU RECENTLY MOVED? PLEASE NOTIFY US.

Pain is a severely debilitating condition (both physically & emotionally). Our goals are to define pain & discuss rationale management This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings. **The program ID # for this lesson is 707-000-08-005-H01-P. Pharmacists completing this lesson by May 31, 2011 may receive full credit.**

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. Describe the physiology of pain.
2. List the types of pain & their respective management.
3. Differentiate between the use of opioids & non-opioids for managing pain.
4. Classify opioids & describe their adverse effects.
5. Discuss the doses of drugs used for pain management.

BACKGROUND

Pain is an unpleasant sensory and emotional feeling that is typically triggered in the nervous system as a result of potential or tissue injury. It may be associated with inflammation, accident, a disease process, or infection. However, it may occur in the absence of a cause. Pain is a reaction by the body to alert the person of the possibility or the presence of an injury. It is highly subjective in nature. It is one of the most difficult medical problems to diagnose and treat. Pain is an unpleasant symptom of illness and one of the most commonly encountered and complex health problems. It varies greatly from one patient to another. It may be sharp or dull, intermittent or continuous, and may last for hours, days or weeks. It can result in loss of job, loss of friends and family relationships. Additionally, it may trigger depression, anxiety, sleep disturbances, disruption of daily activity, fear, anger, frustration and loneliness. In spite of its prevalence, this complicated phenomenon is not fully understood. Recently 77 million Americans complained of pain that persisted for 24 hours. Persons ranging in age from 45 to 64 years are the most likely to report pain lasting more than 24 hours. The least likely to report pain lasting for 24 hours are adults 65 years and older. Women report pain more than men. Compared to other chronic conditions, pain affects more people in the U.S. than diabetes, cardiovascular disease, and cancer. About 32% of adults report that their pain last less than one month, 12% one to three months, 14% three months to one year and 42% longer than one year. The most common types of pain reported by patients who are not suffering from a disease state were low back pain (25%), severe headache (15%), neck pain (15%) and facial pain (4%). Pains due to disease process are common. About 70% of cancer patients experience considerable pain throughout the duration of the disease. Approximately 50% of these individuals experience discomfort during the early stages of the disease, and 75% in the advanced or terminal stages. Between 40 to 50% of cancer patients described the pain as moderate to severe, while 25 to 30% describe it as very severe to excruciating. Approximately 46 million Americans experience pain due to arthritis, rheumatoid arthritis, gout, or fibromyalgia. Approximately 30% of persons 65 years of age and older complained of knee and hip pain or stiffness. The health care costs, lost income, and reduced productivity due to chronic pain have been estimated to be about $100 billion annually. The annual costs of knee replacement surgery were estimated to be $11.9 billion and hip replacement to be about $12.2 billion.

PHYSIOLOGY OF PAIN

Pain is a signal of disease and is usually detected by the nerve endings that are located in the skin, various body tissues and organs. These nerve endings, which are afferent fiber, respond to mechanical, thermal and chemical stimuli. Axons of the nerve endings are fibers that may be very small in diameter and myelinated (A-delta), or unmyelinated (C) fibers which are larger in diameter. Pain evoked by A-delta fibers is usually sharp in nature; whereas, pain generated by C fibers is characterized as a burning pain. Stimulation of these fibers results in transmission of information to the dorsal horn of the spinal cord and to the higher center of the brain. The reticular formation, the periaqueductal gray (PAG) matter and the hypothalamus are involved in the pain mechanism. It should be remembered that inflammatory mediators such as bradykinin, some prostaglandins and leukotrienes contribute to sensitization to pain. Once a tissue is sensitized, any stimulus can result in pain, tenderness and soreness.

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May 2008

TYPES OF PAIN

Pain sensation can be divided into two main categories: **acute** and **chronic.**

Acute pain occurs abruptly as a result of direct response to damage to tissue or to development of a disease state. It usually subsides when the disease or injury are treated. It may occur after surgery or trauma or may be associated with conditions such as myocardial infarction, appendicitis and gall stones. The onset of acute pain is usually sudden, lasts less than six months and subsides when the underlying cause disappears. It is described as sharp in nature, localized, well defined, reversible, and in most cases the cause is known and can be diagnosed. Acute pain may be relieved by using analgesics.

Chronic pain lasts at least 6 months after the body injury has healed. Sometimes healing does not occur, and the cause is often unknown. The pain is diffuse, persistent and may be dull, cramp-like, and difficult to describe. Along with the pain, the person may experience emotional disturbances such as apathy, restlessness, depression, withdrawal, low self-esteem, anger and insomnia. Chronic pain is difficult to treat, and if left untreated may cause fatigue and lowering of pain threshold. Sympathetic output signs are usually absent, and this results in adaptation of the autonomic nervous system.

Chronic pain may be associated with two types of pain:

1- **Neuropathic**: results from damage to nerves which may occur as a result of inflammation or irritation to peripheral nerve endings.

2- **Psychogenic:** a pain disorder due to psychological factors such as mental or emotional problems. Such factors not only may trigger pain, but they may prolong it. Symptoms include headache, muscular, back and stomach pains. Diagnosis of this type of pain is made when the presence of organic disorders affecting a body organ is ruled out. Psychogenic pain can be treated by a psychiatrist in consultation with a family physician or a specialist. Medications used include antidepressants and non-narcotic analgesics.

PAIN MANAGEMENT

The pain sensory system tends to protect the body by detecting, localizing and realizing the processes that cause tissue injuries. Each disease state produces characteristic tissue damage, the type, course and location of pain. Such information is essential in providing indicators as to evaluation of pain and its response to treatment. The most important step in managing acute pain is to remove the cause, once it is diagnosed. Generally acute pain is treatable with analgesics which should be the first line of treatment. Drugs like aspirin and the NSAIDs have similar mechanisms of action. They inhibit cyclooxygenase, and are effective in mild to moderate pain, especially headache and musculoskeletal aches.

Chronic pain differs in symptoms, characteristics, diagnosis, duration and management. Diagnosis of chronic pain is often challenging. Managing cases caused by incurable diseases such as cancer, arthritis, migraine headaches, fibromyalgia and diabetic neuropathy are difficult. Psychological and emotional disturbances may exacerbate pain. In treating chronic pain, utilization of medications, physical therapy, counseling and nerve block may be options that are attempted in order to relieve the patient and improve the quality of life.

Initial pain management often starts with non narcotic analgesics, followed by stepwise inclusion of analgesic adjuncts and opioids. The following is the common step ladder for the use of analgesics:

Step 1: Nonopioid analgesics such as NSAIDs

Step 2: Nonopioid plus adjuncts

Step 3: Weak opioid plus nonopioid and adjuncts

Step 4: Strong opioid plus nonopioid and adjuncts

Analgesic adjuncts include antidepressants, neuroleptics, and anticonvulsants. Studies indicate that about one – third of patients experience acute pain all or most of the time, and that the pain was moderate to

severe in intensity. Other studies have shown that up to 80% of cancer patients do not receive adequate pain relief. Insufficient treatment of pain is considered a major health issue in the U.S. The use of opioid analgesics is often an essential part of pain management. Clinicians should not hesitate to prescribe them, if they are the best treatment of choice.

It is estimated that cancer pain can be acceptably controlled in 90% of cases. The discrepancy between patients in pain, and patients who can be adequately treated, is the result of many barriers and misconceptions surrounding pain management, including: lack of knowledge about pain management approaches, poor communication between patients and physicians, poor communication between different physicians, patient and physician fears about addiction and medication side effects, concerns about controlled substance laws and regulations, and the inability to evaluate pain.

Since fear of addiction is such a common barrier to effective pain management, it is essential that the differences between drug tolerance, physical dependence and addiction be understood. Tolerance means that an increased amount of medication is needed to produce an equivalent effect that resulted with the initial dose. Tolerance to medication side effects means that the intensity of side effects diminishes with continued medication use. Physical dependence means that a withdrawal syndrome results when the medication is abruptly discontinued. Addiction means that a person is psychologically dependent upon a drug. This may be manifested as drug abuse. Psychological dependence results from factors other than medication use (environmental, social, economic, etc.). Thus, patients taking opioids for pain, particularly for chronic pain, do not necessarily become addicts. Studies indicate that the rate of addiction from clinical opioid use is less than 1%. In addition to the barriers and misconceptions previously cited, the following factors may contribute to inadequate pain management: nonindividualized chronic pain therapy, nonsystematic approach to medication selection and dosing, complicated medication regimens and dosing schedules, multiple medication prescribers, and lack of adjustments in the pain therapy plan.

As indicated earlier, it is essential to prevent pain from occurring or recurring. Recommended methods for treating pain include: removal of cause of pain through surgery and splinting; use of non-opioids, opioids and adjunctive medications; regional anesthesia such as epidural infusion, local anesthetics and nerve blocks; physical methods, such as physiotherapy, manipulations and thermal therapy; and, psychological methods. An approach for managing pain may include: pain occurs; treatment begins using non-opioid analgesics; maximizing the dose of a chosen medication before changing to a different non-opioid drug due to inadequate pain relief or intolerable side effects; and, add adjunctive medications as indicated for the pain being treated. If pain persists or increases, opioid analgesics may be indicated to treat mild to moderate pain. The choice of drug and dose should be systematically evaluated before changing to a different opioid. Non-opioid and adjunctive therapies may be continued or added. When acceptable pain relief is achieved, basic pain management principles should be followed: evaluation of pain at regular intervals after starting treatment; individualizing therapy to patient; substitution of drugs within a class should be attempted before changing drug class; therapy regimen should be as easy as possible; medication doses should be scheduled around the clock; and, doses of medication should be available to manage breakthrough pain. Acute pain management is most challenging after surgery or myocardial infarction, in wound treatment, renal colic, and acute low back pain. Therapy is instituted depending on etiology and type of pain.

THERAPEUTIC AGENTS USED FOR PAIN RELIEF

Analgesics drugs that are used to relieve pain may be classified into two major categories: **opioids**, and **non-opioids**.

OPIOID ANALGESICS

These drugs refer to naturally occurring and synthetic chemicals that stimulate (agonist) opiate (opioid) receptors in the brain to produce pain relief without alteration of consciousness. Opiates are derivatives of opium. The major chemicals found in opium are morphine and codeine. The term opioid refers to opium-like or morphine-like effects. Most opioid analgesics provide similar pharmacologic responses, clinical uses and potential for abuse as morphine. At times, the terms opiate and opioid are used interchangeably. The opioids that most of us are familiar with include: morphine, codeine, hydromorphone, oxycodone, meperidine, fentanyl, and methadone.

Pharmacological action: Opioids exert their analgesic action by acting on the CNS. They are agonists (stimulants) at specific receptor binding sites present in the limbic system, thalamus, striatum, hypothalamus, mid-brain and spinal cord. The two most important receptors associated with analgesia are mu and kappa. The mu receptors are located mainly in the limbic system, thalamus, hypothalamus and mid-brain. The kappa receptors are distributed in the cerebral cortex and spinal cord. Opioids are capable of altering perception and emotional response to pain.

Morphine is used to treat severe, acute, chronic or cancer pain. It was isolated from opium in 1806 and has been used as an analgesic ever since. Even though morphine can be prepared synthetically in the laboratory, most of the morphine available today is obtained naturally, because of the difficulty encountered in synthesis. However, minor chemical substitution can be employed to convert morphine to semi-synthetic derivatives such as codeine, hydromorphone, hydrocodone and oxycodone. These analgesics and others, such as the fully chemically synthesized opioids (tramadol, meperidine, methadone, piritramide, and fentanyl), offer no advantage over morphine in the management of chronic pain. In addition to being the first analgesic to be used for chronic pain, it is the standard against which opioids are compared regarding potency and adverse effects. Morphine may be administered orally, intramuscularly, intravenously, subcutaneously, epidurally and rectally. It is distributed well throughout the body, and sufficient amounts cross the blood-brain barrier to produce most of its therapeutic effects. Morphine has a plasma half-life of three hours. It is metabolized completely in the liver and excreted mainly in the kidneys. It is capable of crossing the placental barrier, and is excreted in maternal milk. Initial administration of morphine may cause stimulation of the chemoreceptor trigger zone (CTZ), causing nausea and vomiting. Continued administration of morphine, especially at higher doses, will suppress CTZ, and nausea and vomiting are likely to be prevented. This drug is a potent analgesic employed to relieve severe, acute or moderate to severe chronic pain regardless of its cause or anatomic site. Additionally, it alters perception of pain, thereby reducing distress and discomfort.

Adverse effects of morphine include respiratory depression and, to a lesser degree, circulatory depression. Other side effects include: dizziness, depression, sedation, euphoria, weakness, restlessness, nervousness, nausea, vomiting and constipation. Like all opioids, morphine may cause biliary spasm, urinary retention and oliguria, especially in patients with prostatic hypertrophy. Morphine and other opioids possess the potential for the development of physical dependence and tolerance after prolonged use.

It is usually administered subcutaneously, but may be given by I.M. or slow I.V. infusion to prevent respiratory depression, hypotension and cardiac arrest. If the drug is to be administered repeatedly, then I.M. is the route of choice, since S.C. injection may cause local irritation and induration. For epidural and intrathecal routes, preservative-free injection of morphine should be used. Oral and rectal routes are often employed. Morphine should be given in the smallest effective dose and at a limited frequency in order to reduce the chance for the development of tolerance and physical dependency. Dosage varies from one patient to another depending on the severity of the pain, age, dependence and tolerance and the presence of renal or hepatic impairment. The usual adult S.C and I.M. dosage may range from 5-20 mg every four hours as needed.

However, the usual adult dose is 10 mg every four hours. When administered I.V, a dose of 2.5-15 mg of the drug is diluted in 4-5 ml of sterile water for injection and is given slowly over a period of 4 to 5 minutes. The usual oral dose for adults is 10-30 mg every four hours as needed, while the rectal dose is in the range of 10-20 mg.

Codeine is methylmorphine. It is available in oral solutions, oral tablets and parenteral (S.C & I.M) dosage forms, mostly as sulfate and phosphate salts. It is well absorbed following oral or parenteral administration. It is distributed widely in the body, and excreted through the kidneys. It is used mainly as an analgesic and antitussive, and is considered as a mild analgesic employed mainly for the relief of mild to moderate pain. When used orally, codeine exhibits minimal adverse effects. However, it is recommended that it should be taken with food to reduce gastrointestinal distress, which may be experienced by some patients. Codeine possesses toxicity potential similar to that of other opioids. The usual adult, oral, S.C and I.M. dosage for the relief of mild to moderate pain is 30 mg every 4 hours, as needed.

Hydromorphone is a semi synthetic opioid used mainly as a potent analgesic for the relief of moderate to severe pain. It is well absorbed from the GI tract, has a faster onset of action, and a shorter duration than morphine. Adverse effects such as nausea, vomiting, constipation and euphoria are less pronounced with hydromorphone than with morphine. Hydromorphone may be administered via S.C, I.M or slow I.V. injections as well as orally and rectally. Like all opioids, this drug should be given in the smallest effective dose, and as infrequently as possible. The usual adult dose is 2 mg every 4-6 hours as needed. For severe pain, the dose may be increased to 4 mg every 3 to 6 hours. A similar dose may be given when the drug is administered S.C. or I.M. Larger doses may be given to patients who are tolerant to opioids. A dose of 3 mg inserted rectally in suppository form every 4-6 hours as needed may be used.

Hydrocodone Bitartrate chemically is dihydorcodeinone bitartrate, and is widely used as a mild analgesic for the relief of moderate to severe pain. It is also used as an antitussive. Hydrocodone bitartrate is used orally in the form of tablets in doses ranging from 5-10 mg every 4-6 hours as needed for pain. Currently, it is used in combination with other nonopioid analgesics. Hydrocodone bitartrate possesses toxic potential like other opioids.

Oxycodone is dihydrooxycodeinone that is prepared synthetically. It is approximately 10 times as potent as codeine and is available either alone or in combination with aspirin or acetaminophen. Oxycodone is absorbed readily from the GI tract. It is used in the management of moderate to moderately severe pain. The side effects are milder than those of morphine, but it possesses addictive potential like morphine. It shares the same precaution that should be followed when using other opioids. The usual dose of oxycodone is 5 mg every 6 hours.

Recent reports indicate that there was an increase in the illegal sales of oxycodone extended release tablets and even reports of overdose deaths. When crushed these tablets seemed to provide high absorption rate and strength.

Meperidine Hydrochloride is a synthetic opioid that possesses similarities to morphine. It is well absorbed from the GI tract and is metabolized on first pass through the liver. It is less than one-half as effective as morphine when administered orally as when given parenterally. It acts faster than morphine, but has a shorter duration of action. Meperidine is a potent analgesic employed for the relief of moderate to severe pain. It may be used parenterally for preoperative sedation and in combination with anesthesia to relieve pain during labor. The adverse effects are similar to those of morphine. It is used IM, SC and IV. It is also available in tablets and syrup. Due to its short duration of action, the usual adult dose for pain is 50 to 150 mg every 3 to 4 hours.

Fentanyl Citrate is a synthetic opioid agonist. It is well - absorbed transdermally following the application of a patch - type system. Fentanyl may be utilized transdermally, parenterally and intrabuccally. When

administered parentarelly, it provides faster and more prolonged analgesia than morphine and meperidine. Transdermal preparations are applied in order to provide the drug at a relatively constant rate. However, absorption depends on variation in skin permeability and clearance rate of the drug. The administration of a buccal lozenge matrix results in absorption of the drug through the mucosa and GI tract. Approximately 25% of the dose is absorbed from the buccal mucosa, and the remaining portion from the GI tract. Fentanyl is distributed rapidly through the body following parenteral administration, but slowly into deep fatty tissue into the system. Thus a large dose may cause accumulation of the drug. Fentanyl is a potent analgesic that is mainly used prior, during and after surgery. In addition to the toxic effect that is similar to other opioids, fentanyl can cause adverse effects resulting from topical application of the transdermal system such as erythema, pruritus, edema and papules. Parenteral (I.V, I.M) administration involves the use of 50 to 100 micrograms of the drug 30-60 minutes before surgery. Buccal doses should not exceed 5 micrograms/kg in adults.

Methadone's main use is for narcotic detoxification but can be used as an analgesic in particular for cancer pain. Its long acting properties allow less frequent administration. It is available in oral solution, tablets and IM injections.

NON-OPIOID ANALGESICS

Non - opioid analgesics are used for treating pain that results from injury, surgery, trauma and early stages of cancer. The most commonly used non-opioid analgesics for pain management are aspirin, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). They are effective for mild to moderate pain relief, and are often used in combination with opioid analgesics to reduce the required opioid dose. Acetaminophen and NSAIDs have similar analgesic potency, but acetaminophen does not have peripheral anti-inflammatory effect.

NSAIDs cause analgesia, and stop inflammation by inhibiting cyclooxygenase and stopping the formation of prostaglandins. The site and mechanism of analgesia for acetaminophen remains unclear. It is known to inhibit prostaglandins in the central nervous system, and blocks peripheral pain conduction. NSAIDs are the analgesics of choice for musculoskeletal pain therapy, and are very helpful in treating metastatic bone cancer pain.

NSAIDs are considered to be approximately equipotent at recommended doses. The daily dose should be maximized before adding or changing to other analgesic medications. NSAIDs from different classes should be tried before starting opioid drug therapy. Note that higher NSAID doses prolong the duration of analgesia, and that analgesia duration does not correlate to the drug half-life.

NSAIDs should not be used in patients having thrombocytopenia or renal failure. Gastrointestinal intolerance and potential ulcer formation should be monitored. NSAIDs are highly protein bound, so attention must be paid for the potential for drug – drug interactions with other highly protein bound medications. Acetaminophen should not be used in patients suffering from hepatic failure. Aspirin can cause bronchospasm in patients with a history of asthma, nasal polyps or allergic rhinitis.

CONCLUSION

Pain is a sensation triggered in the CNS to alert the patient to injury or potential of injury. It may be acute and lasts from hours up to months, or it may be chronic and persists for more than several months. It is the most difficult health problem to diagnose and treat. Nonopioid analgesics are used to treat mild pain, whereas opioids alone or in combination with non-opioids are employed for managing moderate to severe pain. A stepwise approach should be followed when treating persisting pain.

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

Describe physiology of pain	Yes	No
List types of pain & management	Yes	No
Differentiate use of opioids & non-opioids for pain management	Yes	No
Classify opioids & describe their adverse effects	Yes	No
Discuss doses of drugs used for pain management	Yes	No

2. Was the program independent & non-commercial Yes No

	Poor			Average			Excellent
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson?_____

5. What did you like least about this lesson?_____

Please Select the Most Correct Answer

1. Pain evoked by A-delta fibers is usually:
   A. Diffused
   B. Dull
   C. Sharp
   D. Burning
2. Which of these contributes to sensitization to pain?
   A. Adrenaline
   B. Bradykinin
   C. Serotonin
   D. Histamine
3. Which of these is not an adverse effect of morphine?
   A. Constipation
   B. Dry mouth
   C. Nausea & vomiting
   D. Euphoria
4. The major chemical(s) in opium is (are):
   A. Morphine & codeine
   B. Morphine
   C. Papaverine
   D. Codeine
5. The Kappa receptors are found in:
   A. Limbic system
   B. Cerebral cortex & spinal cord
   C. Hypothalamus
   D. Mid-brain
6. Initial pain management should begin by taking:
   A. Weak opioids
   B. Non-opioid plus adjuncts
   C. Strong opioid that should be gradually reduced in dosage
   D. Non-opioid analgesic
7. What is incorrect about codeine?
   A. Used for severe pain
   B. Has antitussive activity
   C. Dosage is 30mg every 4 hours as needed
   D. Chemically it is methyl morphine
8. Which statement is correct about oxycodone?
   A. Usual dose is 50mg every 6 hours
   B. Used only for mild pain
   C. 10 times as potent as codeine
   D. Available only as conventional tablet
9. Fentanyl is:
   A. Poorly absorbed intradermally
   B. Not used parenterally
   C. Naturally occurring
   D. Well absorbed intrabucally
10. Methadone:
    A. Has long-acting properties
    B. Used only as narcotic detoxifier
    C. Has no analgesic
    D. Available only as oral solution

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