NARCOTICS

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The term narcotic was obsolete long before the discovery of endogenous opioid-like ligands and receptors for these substances. "Narcotic", derived from the Greek word for stupor and at one time applied to any drug that induced sleep, was for a number of years used to refer to morphine-like analgesics. Today, the term narcotic is no longer useful in a pharmacological context. With the advent of mixed agonist-antagonists, some of which do not suppress morphine-like physical dependence, and with the increasing legal usage of the term for any substance that can cause dependence "narcotic" has little specificity as a pharmacologic term. It is the purpose of this paper to begin an understanding of the many differing compounds or "narcotics" which are used in the management of pain.

Bromptom's cocktail is an oral narcotic mixture used in the management of severe pain. Originally, the formula consisted of 10 mg of morphine, 10 mg of cocaine, alcohol, chloroform water, and syrup. Currently, the term Bromptom's mixture designates any alcoholic solution containing morphine and either cocaine or phenothiazine. Its relevance to modern day medicine is that this mixture established the value of regular administration of narcotic analgesics for pain relief, and thus is the figurative "grandfather" of many of today's narcotic analgesics.

Narcotic analgesics are classified as agonists, mixed agonist-antagonists, or partial agonists by their activity at opioid receptors. Five major categories of opioid receptors are known: mu (M) kappa (K) sigma (Σ) delta (Δ) and epsilon (E). Actions of the currently available narcotic analgesics can be defined by their activity at three specific receptor sites: (MKΔ).

The mu receptors mediate morphine like supra-spinal analgesia, euphoria and respiratory and physical depression. The kappa receptors mediate pentazocine like spinal analgesia, sedation and miosis. The sigma receptors mediate dysphoria, physcomimetic effects (i.e., hallucinations) and respiratory and vasomotor stimulation caused by drugs with antagonist activity. Morphine-like narcotic agonists have activity at the mu and kappa receptors, and possibly at the delta receptor as well. Narcotic agonists include natural occurring opium alkaloids (i.e., morphine and codeine), semisynthetic analogs (i.e., hydromorphone, oxymorphone and oxycodone) and synthetic compounds (i.e., meperidine, levorphanol and methadone).

Mixed agonist-antagonist drugs, (i.e., nalbuphine and pentazocine) have agonist activity at some receptors and antagonist activity at other receptors; also included in this group are the partial agonists (i.e., butorphanol and buprenorphine).

Narcotic antagonists (naloxone) do not have agonist activity at any of the opioid receptor sites. Antagonists block the opiate receptor, inhibit pharmacological activity of the agonist and precipitate withdrawal in dependent patients. Opiate receptors in the CNS mediate analgesic activity. Narcotic agonists occupy the same receptors as endogenous opioid peptides (enkephalins and endorphins) and both may alter the central release of neurotransmitters from afferent nerves sensitive to noxious stimuli.

Narcotics, as a group, have a variety of secondary pharmacological effects including:

CNS: Euphoria, drowsiness, apathy, mental confusion. Nausea and vomiting are caused by direct stimulation of the emetic chemoreceptors located in the medulla.

RESPIRATORY: Because of reduced sensitivity of the respiratory center to carbon dioxide, depressant effects first diminish tidal volume, then respiratory rate.

CARDIOVASCULAR: Peripheral vasodilation, reduced peripheral resistance and inhibition

of baroreceptors. Orthostatic hypotension and fainting may occur.

GASTROINTESTINAL: Inhibits peristalsis which may induce constipation and spasm of the Sphincter of Oddi.

GENITO-URINARY: Urinary retention may occur with increased bladder sphincter tone.

Generally, IV administration is most reliable and rapid. Intramuscular or subcutaneous use may delay absorption and peak effect, especially with impaired tissue perfusion. Many agents undergo a significant first pass effect, and all are metabolized by the liver and excreted primarily in the urine.

NARCOTIC AGONIST ANALGESICS

Morphine Sulfate

Morphine sulfate is the principal opium alkaloid and is indicated for relief of moderate to severe acute and chronic pain. It also is indicated preoperatively to sedate and allay apprehension, facilitate induction of anesthesia and reduce anesthetic dosage. Morphine sulfate is not as potent orally because of its first pass metabolism. Oral administration is 1/3 to 1/6 as effective as parenteral dosage. Recommended dosage is as follows:

Oral: 10 - 30 mg every 4 hours or as directed. Controlled release tablets are 30 mg every 8 - 12 hours. It is recommended not to chew or crush tablets.

S.C/IM: 10 mg (5 - 20 mg) / 70 kg adult every 4 to 6 hours up to 15 mg.

I.V.: Continuous IV infusion can be administered variably by means of PCA (Patient Controlled Analgesia).

Hydromorphone HCL (Dilaudid)

Hydromorphone is another potent analgesic which is used for patients who have undergone significant reconstructive procedures and more extensive dissection. Generally, this agent is more potent than Demerol and is often substituted for other less effective narcotic agents. Administration and dosage is as follows:

Oral: 2 mg every 4 to 6 hours. More severe pain is dosed 4 mg every 4 to 6 hours as needed.

Parenteral: 1 to 2 mg SC or IM every 4 to 6 hours as needed. For severe pain administer 3 to 4 mg every 4 to 6 hours as needed. May be given by slow IV injection over 2 - 5 minutes.

Meperidine HCL (Demerol)

Meperidine HCL is a narcotic analgesic with multiple actions qualitatively similar to those of morphine. Meperidine may produce less intense smooth muscle spasm and less constipation and depression of the cough reflex than equi-analgesic doses of morphine.

For relief of pain, the dosage must be individualized. While SC administration is suitable for occasional use, IM administration is preferred for repeated doses. If IV administration is required, decrease the dosage and inject very slowly, preferably using a diluted solution. Demerol is less effective when given orally. Recommendations include reduction of the dose by approximately 25 - 50% when administering concomitantly with phenothiazine or other tranquilizers. The recommended dosing is as follows:

Adults: 50 to 150 mg IM, SC or orally every 3 to 4 hours as needed.

Children: 1 to 1.8 mg/kg (0.5 to 0.8 mg/lb) IM, SC or orally up to adult dose, every 3 to 4 hours as needed.

When using Meperidine to support anesthesia and sedation for reduction of dislocations or painful wound debridement it is recommended to administer in doses diluted to 10 mg/ml by slow IV injection. Individually titration is recommended and supportive measures should be readily available. An absolute contraindication of Demerol is the patient who has taken an MAO inhibitor within 14 days.

Codeine

Codeine is a narcotic analgesic and anti-tussive that pharmacologically resembles morphine but has a milder action. It is widely used as an anti-tussive (cough suppressant) because of its low incidence of adverse reactions at the usual anti-tussive dose. Its primary indication for the relief of mild to moderate pain is outlined as follows:

Adults: 15 60 mg every 4 to 6 hours, PO SC, IM or IV. It is recommended not to exceed 120 mg in 24 hours.

Children: In children greater than 1 year of age, 0.5 mg/kg or 15 m2 of body surface every 4 to 6 hours SC, IM or orally. IV usage is not recommended in children.

Propoxyphene (Dextropropoxyphene)

Propoxyphene is a centrally acting narcotic analgesic structurally related to methadone. It is generally 1/2 to 2/3 as potent as codeine and is no more, and possibly less effective than 30 to 60 mg of codeine or 600 mg of aspirin. Its general indication is for relief of mild to moderate pain, however significant risk has been demonstrated with the use of this drug with alcohol. Overdosage alone or in combination with alcohol has lead to many deaths. Judicious prescribing of propoxyphene is essential for safety.

Propoxyphene HCL (Darvon)

Usual dose is 65 mg every 4 hours as needed, not to exceed 390 mg per day. (Oral administration only).

Propoxyphene Napsylate (Darvocet N)

Usual dose is 100 mg every 4 hours as needed, not to exceed 600 mg per day. (Oral administration only).

Because of molecular weight differences, 100 mg of propoxyphene napsylate is required to supply propoxyphene equivalent to 65 mg of the HCL salt. Many other drugs of analgesic quality are found under the heading Narcotic Agonist Analgesics and should be reviewed prior to prescription.

NARCOTIC AGONIST ANTAGONIST ANALGESICS

Narcotic agonist-antagonist analgesics compete with other substances at the mu (M) receptor. These receptors mediate morphine-like supraspinal analgesia, euphoria and respiratory and physical depression. Two types of narcotic agonist-antagonists are:

1. drugs which are antagonists at the mu (M) receptor and are agonists at the other receptors (i.e., pentazocine).
2. Partial agonists (i.e., buprenorphine) which have limited agonist activity at the mu (M) receptor.

The narcotic agonist-antagonist analgesics are potent agents with a lower abuse potential than pure narcotic agonists.

Pentazocine (Talwin)

Pentazocine weakly antagonizes the effects of morphine, meperidine and other opiates at the mu (M) receptor. Presumably, it exerts its effects on the kappa (K) and sigma (Σ) opioid receptors. Along with its analgesic properties, it is also a sedative. Parenterally, 30 mg is usually as effective an analgesic as 10 mg of morphine or 75 to 100 mg of meperidine. Orally, a 50 mg dose is equivalent to 60 mg of codeine.

Also available is Talwin NX which contains naloxone, and produces analgesic effects when administered orally. Talwin is a drug with a high abuse potential and illicit usage is well documented. Many drug interactions are associated with Talwin and caution should be given upon prescription. Administration and dosage is as follows:

Adults: Orally, 50 mg every 3 to 4 hours and increase to 100 mg if necessary, without exceeding a total daily dosage of 600 mg.

Children: Usage in children is not established and should be avoided.

Butorphanol (Stadol)

This agent is a potent analgesic with both narcotic agonist and antagonist activity. On a weight basis the analgesic potency of butorphanol appears to be 3.5 to 7 times that of morphine, 30 - 40 times that of meperidine and 20 times that of pentazocine. The pharmacokinetics of Stadol includes rapid onset. In fact, onset of analgesia is approximately 10 minutes following IM administration, and peaks at 30 - 40 minutes. Its half-life is 2.5. hours. Our experience with this medication has been less than the described duration of analgesia of 3 to 4 hours.

Adults: IM - usually 2 mg every 3 to 4 hours as needed. Dosage range is 1 to 4

mg every 4 hours. It is recommended not to exceed single doses of 4 mg. IV: Usual single dose is 1 mg every 3 to 4 hours as needed, and dosage range is 0.5 to 2 mg every 3 to 4 hours.

Nalbuphine (Nubain)

This agonist-antagonist medication has actions similar to phenanthrene derivatives, oxymorphone and naloxone. Its analgesic potency is essentially equivalent to that of morphine and about 3 times that of Talwin. Nubain does not significantly increase pulmonary artery pressure, systemic vascular resistance or cardiac work as do most other agonist-antagonists. Administration and dosing is as follows:

Adults: Usual dose is 10 mg/70kg adult given SC, IM or IV every 3 to 6 hours as necessary individualizing dosing schedules accordingly.

Children: No established guidelines are available.

If the patient has recently received a narcotic such as morphine, meperidine codeine, or another agent with similar duration of activity, administer 1/4 the anticipated dose of nalbuphine.

Ketorolac Tromethamine (Toradol)

Ketorolac tromethamine (Toradol) is manufactured by Syntex but also marketed by Roche and is the first parenteral nonsteroidal anti-inflammatory drug (NSAID) to become available for use in the USA. Other parenteral NSAIDs are available in other countries of the world, but low potency, poor aqueous solubility, and substantial tissue irritation have limited their usefulness.

Like other NSAIDs Toradol has anti-inflammatory, antipyretic and analgesic activity. Assays in animals suggest that compared with other NSAIDs, Toradol is relatively more effective as an analgesic than as an anti-inflammatory agent. Standard tests in mice, where the relative potency of aspirin was assigned a value 1, the relative potency of ketorolac was 350. Values for other NSAIDs include 0.8 for phenylbutazone, 7 for naproxen, and 60 for indomethacin. Two single dose, double blind, six hour trials in patients with moderate to severe postoperative pain found 30 mg of IM ketorolac superior to 6mg of morphine and at least comparable to 12 mg of morphine. The onset of analgesia with ketorolac was comparable to that of morphine, but the peak effect occurred later (about two hours after injection), and the duration of action was longer, (about five to six hours).

The recommended initial dosage of ketorolac for the short term management of pain is a 30 or 60 mg intramuscularly loading dose, followed every six hours with 15 or 30 mg as needed to control pain. The maximum recommended total daily dosage is 150 mg in the first day and 120 mg/day thereafter. At this institution, we commonly use Toradol in conjunction with I.M. Demerol and have had excellent success in managing post operative pain in the initial 72 hours after surgery. Many times the patient's need for Demerol decreases when Toradol has been added. It is also recommended for patients weighing less than 50 kg, those with reduced renal function, and in the elderly that the lower end of the dosage range be utilized.

The adverse effects of Toradol intramuscularly have been similar to those reported with the short term use of oral NSAIDs. In comparative trials, Toradol caused fewer adverse effects and was discontinued less often than either morphine or meperidine. The most common adverse effects of ketorolac were drowsiness, dyspepsia, gastrointestinal pain, and nausea. Less frequent side effects included edema, diarrhea, dizziness, headache and sweating. Pain at the injection site was reported less frequently than with morphine.

The cost of Toradol will vary slightly from region to region however, according to Syntex ten prefilled 60 mg syringes cost approximately $58.50. In comparison the pharmacy cost of a 6mg or 12 mg dose of morphine is approximately 50 cents.

In conclusion, ketorolac (Toradol) appears to be as effective as morphine or meperidine for short-term relief of moderate to severe postoperative pain, without respiratory depression or the other disadvantages of opiates. Since this drug is relatively new, care should be taken when prescribing. The reader is referred to current literature for updated information.

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