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PHARMACOLOGY OF OPIOIDS – PART 2 ANAESTHESIA TUTORIAL OF THE WEEK 67

3rd SEPTEMBER 2007

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INDIVIDUAL OPIOIDS

Morphine

Morphine is a naturally occurring phenanthrene derivative. It is the standard drug against which all other opioids are compared.

Dose: Morphine can be given orally, intramuscularly (IM), intravenously (IV), subcutaneously (SC), rectally, epidurally and intrathecally.

The intramuscular dose is 0.1-0.2 mg/kg, time to peak effect is 30-60 minutes and duration of action is 3-4 hours. Intravenous administration should be titrated to effect (usually 1-2mg boluses), but the total dose is similar. The onset of action is slightly more rapid with following IV administration, as the main factor responsible for its latency is low lipid solubility and slow penetration of blood brain barrier. Morphine may be given epidurally at 10% and intrathecally at 1% of the parenteral dose.

Pharmacokinetics: Morphine is extensively metabolised by the gut wall and the liver to morphine-3-glucuronide (M3G) (70%), morphine-6-glucuronide (M6G) (10%) and to sulphate conjugates. M6G is 10-20 times more potent than morphine and is normally excreted in urine. It accumulates in renal failure and accounts for increased sensitivity to morphine. Neonates are more sensitive than adults to morphine due to reduced hepatic conjugating capacity. In the elderly, owing to reduced volume of distribution, peak plasma level of morphine is higher compared to younger patient.

Effects: The main effects are mediated through MOP receptors. It is a potent analgesic with good sedative and anxiolytic properties. It may cause euphoria, dysphoria and hallucination. It produces respiratory depression and cough suppression. It has minimal effect on cardiovascular system and may produce bradycardia and hypotension. Nausea and vomiting are common side effects. Histamine release may lead to rash, itching and bronchospasm (in susceptible patients). Meiosis is common. Tolerance and dependence may develop.

Papaveretum

Papaveretum is a preparation containing a mixture of hydrochloride salts of opium alkaloids: morphine hydrochloride, codeine hydrochloride and papaverine hydrochloride. Prior to 1993, the preparation also contained noscapine, however this was removed after it had been shown to be teratogenic in animal studies.

Dose: It can be given subcutaneously, intramuscularly or intravenously.

15.4 mg of papaveretum contains 10 mg of morphine. It is used for moderate to severe pain and preoperative sedation.

Effects: In comparison with morphine, it provides greater degree of sedation for a given level of analgesia with fewer gastrointestinal side effects. Higher doses of papaveretum are associated with transient but severe headache. This effect, linked most likely to its papaverine content, reduces the compound's addiction potential. Most anaesthetists feel that the added expense of the mixture is not justified because in the concentration used, morphine is the only active ingredient.

Codeine

Codeine is a natural opioid and one of the principal alkaloids of opium. It has very low affinity for opioid receptors.

Dose: Can be given orally and IM. The dose for an adult is 30-60 mg by either route and can be repeated at 6 hours interval, if required. Varying doses of codeine (8-30 mg) are commonly incorporated with NSAIDs in compounds employed in the treatment of mild to moderate pain. Codeine is also used in antitussive and antidiarrhoeal preparations.

Pharmacokinetics: Oral bioavailability of codeine is 50%. About 10% is metabolised to morphine and the rest is metabolised to inactive conjugated compounds. The metabolism to morphine depends on an isoform of cytochrome P450, which exhibits polymorphism, so that poor metabolizers (approximately 10% people) may experience minimal pain relief.

Effects: It causes little euphoria and has low abuse potential. Codeine is less sedative and less likely to cause respiratory depression than morphine. It may cause disorientation and excitement. Constipation is common side effect. Dihydrocodeine is a semi-synthetic derivative of codeine with similar pharmacologic effects. Oxycodone is more effective, but has higher abuse potential.

Diamorphine (heroin)

A semi-synthetic opioid, the diacetylated analogue of morphine. It is 1.5-2.0 times more potent than morphine. It is a pro-drug and is converted the active components of acetylmorphine and morphine by esterases in liver, plasma and central nervous system.

Dose: Diamorphine can also be given by the same routes as morphine in approximately half the dose. Due to its higher lipid solubility, it is less likely than morphine to cause delayed respiratory depression when used epidurally or intrathecally. It can be administered as hydrochloride salt by IM or SC infusion in a smaller volume of solution than equivalent dose of morphine. This is an important consideration for patients with terminal malignant disease who may require large doses of opioid for pain relief.

Pharmacokinetics: Diamorphine is 200 times more lipid soluble than morphine and, therefore, pass more rapidly across the blood-brain barrier into the CNS where it is converted to morphine. Therefore, it has more analgesic potency and rapid onset of action than morphine. Because of the extensive first pass metabolism, it has low bio-availability.

Effects: It shares common opioid effects with morphine. It is associated with an increased tendency to cause euphoria and dependency. May cause less nausea and vomiting than morphine.

Pethidine

It is a synthetic phenylpiperidine derivative and was originally developed as an antimuscarinic agent.

Dose: Pethidine is available as 50 mg tablets and ampoules of different strength (10 mg/ml and 50 mg/ml). For acute pain, it can be administered orally (50-150 mg), SC (50-100 mg), IM (50-100 mg) or IV (25-100 mg). The doses can be repeated every 4 hours.

Pharmacokinetics: Pethidine is 30 times more lipid soluble than morphine. Oral bio-availability is 50%. It is metabolised in the liver by ester hydrolysis to norpethidine and pethidinic acid that are excreted in urine and therefore accumulate in renal failure. At higher concentration, norpethidine can produce hallucination and convulsions. Pethidinic acid is an inactive compound. Pethidine is often used for labour analgesia. It readily crosses placenta, and a significant amount reaches to the foetus over several hours.

Effects: There are some pharmacological differences from morphine. It produces tachycardia, dry mouth and less marked meiosis. However, significant fall in BP may occur when pethidine is administered to elderly or hypovolaemic patients. It may produce less biliary tract spasm than morphine. Pethidine is absolutely contraindicated in patients on monoamine oxidase inhibitors (MAOI), as serious side effects like hypotension or hypertension, hyperpyrexia, convulsion and coma may occur. The underlying mechanism is not clear but may involve reduced metabolism of pethidine by MAOI and pethidine's effect on turnover of 5- hydroxytryptamine in the brain.

Fentanyl

It is a synthetic phenylpiperidine derivative. It is 100 times more potent than morphine.

Dose: It is available as colourless solution for injection in 2 and 10 ml ampoules containing 50 microgram per ml. When given in small doses (1-2 microgram/kg), it has rapid onset and short duration of action (30 minutes). Such doses are used intravenously for pain associated with minor surgery. In small doses it has little sedative effect. Higher doses are used to obtund sympathetic response to laryngoscopy and intubation. Fentanyl has been used to augment effects of local anaesthetics in spinal and epidural analgesia at 10-25 microgram and 25-100 microgram doses respectively. Fentanyl is also available as transdermal patch for chronic pain conditions and as lollipop to premedicate children.

Pharmacokinetics: Fentanyl is 500 times more lipid soluble than morphine, consequently it is rapidly and extensively distributed in the body (volume of distribution 4 L/kg). At small doses (1-2 microgram/kg), plasma and CNS concentration fall below an effective level during rapid distribution phase. However, following prolonged administration or with high doses, its duration of action is significantly prolonged. In these circumstances, the distribution phase is complete while the plasma concentration is still high. Recovery from the effect of the drug then depends on its slow elimination from the body (terminal half life 3.5 hours). Fentanyl is predominantly metabolised in the liver to norfentanyl which is inactive. The metabolite is excreted in the urine over few days.

Effects: Many properties of fentanyl are similar to morphine. It produces respiratory depression in dose-dependent manner. Large doses (50- 100 microgram/kg) have been used for cardiac surgery to obtund metabolic stress response. At such high doses, sedation is profound and unconsciousness may occur, muscular rigidity of the chest wall may affect ventilation.

Alfentanil

Alfentanil is synthetic phenylpiperidine derivative structurally related to fentanyl; it has 10-20% of its potency.

Dose: Alfentanil is available as colourless solution in the concentrations of 500 microgram/ml or 5 mg/ml. It may be administered intravenously as either bolus or continuous infusion. Bolus doses (10 microgram/kg) are useful for short term analgesia and attenuation of cardiovascular response to intubation. Continuous infusions (0.5-2.0 microgram/ kg/min) are used in the intensive care unit for sedation in patients on mechanical ventilation.

Pharmacokinetics: Although it has much lower lipid solubility than fentanyl, more alfentanil is present as unionised form compared to fentanyl (89% compared to 9%); consequently, its onset of action is more rapid. Also, because of its lower lipid solubility, less alfentanil is distributed to muscles and fat. Hence, its volume of distribution is relatively small and more of the dose remains in blood from which it can be cleared by the liver. Even though alfentanil has a lower clearance rate, this is more than offset by its reduced volume of distribution and its half life is relatively short.

Effects: Most effects of alfentanil are similar to fentanyl but with quicker onset and shorter duration of action.

Remifentanil

It is a synthetic phenylpiperidine derivative of fentanyl with similar potency but is ultra short-acting.

Dose: It is available as white crystalline powder in glass vial containing 1, 2 or 5 mg remifentanil hydrochloride. A range of infusion rates (0.05- 2.0 microgram/kg/min) are used during maintenance of anaesthesia with controlled ventilation.

Pharmacokinetics: Remifentanyl is rapidly broken down by non-specific plasma and tissue esterases resulting in a short elimination half life (3-10 minutes). It is context insensitive, in that the half life, clearance and distribution are independent of duration and strength of infusion.

Effects: Certain properties of remifentanyl like rapid onset, rapid offset, organ independent metabolism and lack of accumulation make it suitable for use during various surgical procedures. However, it should be used cautiously at higher rates of infusion as serious side effects for example bradycardia, hypotension, apnoea and muscle rigidity may occur. Since there is no residual effect, alternative postoperative analgesic regimen should be established before infusion is terminated.

Tramadol

Tramadol is phenylpiperidine analogue of codeine. It is weak agonist at all opioid receptors with 20-fold preference for MOP receptors. It inhibits neuronal reuptake of norepinephrine. It potentiates release of serotonin and causes descending inhibition of nociception.

Dose: Oral and parenteral dosage requirements are similar, 50-100 mg 4 hourly.

Pharmacokinetics: Tramadol has high oral bioavailability of 70% which can increase to 100% with repeated doses due to reduction in first pass effect. It is 20% bound to plasma proteins. It is metabolized in the liver by demethylation. In to a number of metabolites only one of them (O-desmethyltramadol) has analgesic activity. Its volume of distribution is 4.0litres/kg and its elimination half-life is 4-6 hours.

Effects: In equi-analgesic dose to morphine, tramadol produces less respiratory and cardiovascular depression than morphine. Constipation is less common. However, tramadol shares most of the common side effects of other opioids (e.g. vomiting, drowsiness and ambulatory dizziness). Tramadol is contra-indicated in patients on MAOI or with a history of epilepsy.

Methadone

A potent opioid analgesic that is well absorbed with good oral bioavailability (75%). However, its main use is as a substitute for opioids for example diamorphine (heroin) in addicts because its slow onset and offset reduces the incidence of withdrawal symptoms. It is itself addictive.

PARTIAL OPIOID AGONISTS

This group of drugs have affinity for opioid receptors but low intrinsic activity compared to full agonists. Because of their reduced activity, they are able to antagonise or reduce the responsiveness of a pure agonist like morphine when acting at the same receptor. In other words, a higher dose of a pure agonist is required in presence of partial agonist, in order to obtain full agonist response. They can be further divided into two groups:

1. Mixed agonist-antagonist: They exert agonist effects at one opioid receptor and antagonistic effects at the other. Examples- pentazocine, nalbuphine and meptazinol.

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2. Drugs that do not display antagonistic effects but have diminished effects at opioid receptors. Example- buprenorphine.

Meptazinol

Meptazinol is a synthetic analgesic with mixed agonist-antagonist activity at opioid receptors. It also has an action via central cholinergic pathways that may contribute to analgesia. It produces less respiratory depression because of its selectivity for MOP-1 receptors. Its main disadvantage is a high incidence of nausea and vomiting, that can be reduced by administration of antimuscarinic drugs. It is one-tenth as potent as morphine. It has rapid onset of action that lasts for 2-4 hours.

Buprenorphine

Buprenorphine is 30 times more potent than morphine. It is highly lipid soluble, and is well absorbed sublingually. It has low oral bioavailability. Although its terminal half-life is 3-4 hours, it has a much longer duration of action (upto 8 hours).

In general, buprenorphine and morphine produce similar effects and side effects. As buprenorphine has extremely high affinity for MOP receptors, its effects are not completely reversed by naloxone (see opioid antagonists). Respiratory depression may need to be treated with doxapram. Nausea and vomiting are severe and prolonged.

Pentazocine

Pentazocine has 25% of the analgesic potency of morphine. It is not very effective in relieving severe pain, and this may be partly because of absence of euphoriant effect. It produces an increase in heart rate and BP. Nausea, vomiting, bizarre dreams and hallucination are more common than morphine.

OPIOID ANTAGONISTS

Naloxone and its longer acting derivative naltrexone occupy opioid receptors, but they have essentially no intrinsic activity at these receptors. Moderate doses administered in absence of an opioid produce no effect; large doses, however, may have effects in which antagonism of endorphins may play a role.

Naloxone

Naloxone is a pure opioid antagonist and will reverse opioid effects at MOP, KOP and DOP receptors, although its affinity is highest at MOP receptors.

It is the drug of choice for the treatment of opioid induced respiratory depression. The usual dose is 200-400micrograms intravenously, titrated to effect. Smaller doses (0.5-1.0 microgram/kg) may be titrated to reverse undesirable effects of opioids for example itching associated with the intrathecal or epidural administration of opioids, without significantly affecting the level of analgesia. The duration of effective antagonism is limited to around 30 minutes and therefore longer acting agonists will outlast this effect

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and further bolus doses or an infusion (5-10 microgram/kg/hr) will be required to maintain reversal. Caution must be used in opioid addicts as giving naloxone may cause an acute withdrawal state with hypertension, pulmonary oedema and cardiac arrhythmias. Antanalgesic effects may be observed in opioid naïve subjects who are given naloxone.

Naltrexone

Naltrexone has similar mechanism of action, but has few pharmacokinetic advantages compared to naloxone. It has longer half-life and is effective orally for up to 24 hours. It has been used to treat opioid addiction and compulsive eating with morbid obesity.

FURTHER READING

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