Fentanyl for Pain Control in Special Operations

Robert F. Kacprowicz, MD; Troy R. Johnson, MD; Dan S. Mosely, MD

Abstract

Opiate medications have been used for the control of severe pain due to combat trauma for hundreds of years. Morphine has long been the drug of choice for use on the battlefield, but it has several limitations which can make it difficult to use in modern warfare. Since its discovery in 1963, fentanyl has gradually emerged as one of the most effective alternatives to morphine. With fewer adverse effects and multiple routes of administration, fentanyl appears to be a very effective choice for the management of moderate to severe pain due to combat trauma. Available data support the use of fentanyl in Special Operations, but only after a thorough review of the pharmacology, adverse effects, dosing, and routes of administration.

Introduction

Opiates have been the analgesic of choice for the relief of moderate to severe pain for over 3500 years and have been the drug of choice for relief of pain from combat related injuries since the American Civil War. The first opiate used was a simple extract from the poppy plant, *Papaver somniferum*. The list of currently available opiates has expanded to include not only derivatives of the original poppy plant, but also very potent, purely synthetic compounds with over a thousand times the potency of the original formulation. Along with increased potency have come variable methods of administration. Oral, IM, IV, transdermal, transbuccal, and transnasal routes are now used for delivery of a variety of opiate compounds. This article will discuss a brief background of opiates, their pharmacology, side-effects, and precautions. We will focus on fentanyl in its two distinct delivery forms and their use in the Special Operations and prehospital environments.

Background

Opium and opiates were first noted in 1500 BC in the Ebers Papyrus' description of a poppy extract used to soothe crying children in ancient Egypt.[1] The writings of Theophrastus (3rd century B.C.) note the term opium from the Greek word for juice of a plant.[2] Hippocrates (BC 460 to 377 BC) and Galen of Pergamon (AD 131 to 200) likewise used opium for a wide variety of ailments.[3] The Swiss physician Paraclesus is credited with extracting the alkaloid laudanum by placing opium into brandy in the sixteenth century.[1] In 1804, German pharmacologist Setürner isolated and purified morphine, one of the more than 20 distinct alkaloids found within crude opium.[4] This derivative saw widespread use by the Union Army, via subcutaneous injection, during the Civil War.[5] This continued throughout the nineteenth century, and many of the derivatives were exploited for their analgesic and euphoric properties. In 1898, Bayer and Company introduced a semisynthetic diacetylated morphine, promoting it as a less addictive but equally effective antitussive.[6] The trade name given to the new drug was heroin, and by 1912, it was more readily available over-the-counter than codeine and had proved to be more potent than morphine.[7] Recognition of heroin's high abuse potential led to the Harrison Narcotic Control Act of 1914, which ultimately served to restrict the sale of narcotics and preceded an outright ban on heroin distribution in 1924. Dr. Everette May and Dr. Eddy worked to develop opiates that relieved pain without the potential for abuse and to discover synthetic substitutes for opiates — called opioids. Based on May's work on benzomorphans, the drug pentazocine was introduced in the 1960s. Pentazocine was the first drug used in clinical practice as a painkiller which combined the pain-relieving effects of morphine with the effects of opiate antidote.[8] In 1960 Dr. Paul Jannsen, working for Jannsen Pharmeceutica, formulated N-(1-phenethyl-4-piperidyl)-propionalide citrate. This compound proved to be much more potent than morphine and exhibit significantly less side-effect. In 1963 it was released to the public and fentanyl, the first fully synthetic highly lipophilic phenylpiperidine derivative, was born.[9]

Opioid Pharmacology and Pathophysiology

The natural opiates, morphine and codeine, are the dried extract from the seedpod of the poppy plant *Papaver somniferum*.[10] Semisynthetic opioids, heroin, naloxone, and oxycodone, are created by the chemical alteration of opium's alkaloids.[10] Synthetic opioids, methadone, and fentanyl, demonstrate pharmacologic properties of opium but are purely synthetic and synthesized de novo.[1]

Opioids can be absorbed by virtually any method but have a significant first-pass metabolism by the liver. Oral administration therefore requires a significantly larger dose in order to achieve similar effects. Most opioids undergo hepatic conjugation with glucuronic acid, undergo hepatic oxidation, or are hydrolyzed by tissue esterases to form metabolites that are excreted by the kidney.[10] The presence of active metabolites varies among the different opiods and greatly affects the potency and duration of their effects.

Opioids produce their effects by interacting with specific receptors within the central and peripheral nervous systems. They resemble the body's three known endogenous opioid peptides: enkephalins, endorphins, and dynorphins.[11] Three major classes of opioid receptors mediate the pharmacologic effects: mu (μ), kappa (κ), and delta (δ).[10,11] The specific analgesic effects of opioids are a function of several factors: affinity for the receptor, intrinsic receptor activity, presence of active metabolites, and genetic variation within the population.[12]

In general opioids hyperpolarize the nociceptive (pain) neurons and inhibit neurotransmitter release. Opioid-receptor activation results in inhibition of adenyl cyclase activity, creating K+ influx, and inhibiting Ca++ influx. This hyperpolarizes the cell thus raising the threshold for activation.[10,11] The clinical effect is reduction of pain perception while still maintaining sensory perception.

With the identification of the opiate receptors in 1973 our understanding of the types of receptor and effects has greatly increased.[13] Opioids typically bind to more then one receptor, but the affinity to the different opioids receptors produces different effects. Mu (μ1) is associated with morphine-like analgesia. Mu (μ2) receptors, found mostly in the supraspinal and spinal cord, produce the euphoric effect and are also responsible for respiratory depression, miosis, inhibited GI motility, bradycardia, and psychological aspects of chemical dependence.[12] Kappa (κ) receptors are found in the spinal cord and produce the effects of dysphoria and depersonalization. The delta (δ) receptors contribute to spinal analgesia and respiratory depression but are the least understood of the opioids receptors.[14,15] The euphoric and sedative effects of the mu (μ2) and delta (δ) -receptors appears to be mediated by the release of dopamine in the mesolimbic area of the brain.[1]

Opioids can be broken down into three functional groups: agonist, antagonist, and mixed (agonist-antagonist). Agonists primarily bind on μ and κ receptors and result in the effects outlined above. In contrast, opioid antagonists (Naloxone, Narcan) occupy the receptors but do not activate the receptors. Antagonists competitively block receptor activation and inhibit binding of opioid agonists. Mixed agonist-antagonist opioids (Buprenorphine [Buprenex], Butorphanol [Stadol], Nalbuphine [Nubain]) produce varied effects depending on the predominance of agonistic or antagonistic activities in the different types of receptors. Typically mixed agonist-antagonist produce a certain level of receptor activation, and analgesia, but create a "ceiling" effect were further activation is inhibited. Thus, mild to moderate pain can be controlled but further administration of the medication will not produce additional relief.[10,11]

Adverse Effects of Opioids

The adverse clinical effects of opioids are generally mediated through a combination of opioid receptor stimulation, especially the μ2 receptor, and histamine release. Major side-effects are respiratory depression, CNS depression, and indirect cardiovascular effects.

The most common cause of death from opiate toxicity is respiratory depression resulting in respiratory arrest. Respiratory depression from opioids appears to be due to a combination of both central and peripheral effects. Peripheral chemoreceptor-mediated ventilatory responses are blunted and the central respiratory centers of the medulla oblongata appear to be affected as well.[11] Respiratory depression can initially be subtle and manifest as small decreases in tidal volume; therefore, reliance solely on respiratory rate to detect respiratory depression can be unreliable and should be discouraged.[16,17] Close monitoring for respiratory compromise through clinical and adjunctive means (Pulse OX, end tidal CO_2) is warranted.

Decreased levels of consciousness from central nervous system depression range from mild sedation to coma. Profound CNS depression can impair the gag response and coupled with centrally mediated nausea and vomiting may result in pulmonary aspiration of gastric contents.[11]

Most opiates also have indirect cardiovascular effects though histamine release. The opioid-mediated release of histamine is via an undefined, direct, nonallergic mechanism.[18] This can result in itching, warmth, and urticaria. Histamine release also induces vasodilation and increased peripheral vascular permeability that can pre-

cipitate hypotension and edema. Pretreatment with a combination of H1 and H2 antagonists can decrease these hemodynamic effects.[11]

The miosis that is seen with opiate use generally occurs within five minutes of administration and can last up to six hours. This is primarily from μ-related stimulation of the visceral nuclei of the oculomotor nuclear complex and the parasympathetic nerve that innervates the pupil. [11]

FENTANYL

After release to the medical community in 1963, fentanyl was recognized for possessing potent analgesic qualities without histamine release. Medical professionals quickly came to appreciate the reduced cardiovascular effects seen with morphine.[19] The lack of side-effects led to rapid adoption in operative pain management and sedation. As civilian trauma management became more centralized, fentanyl became the drug of choice for the management of trauma in the peri-operative setting. Providers in austere settings did not adopt fentanyl as quickly; however, primarily due the IV-only nature of the early preparation and secondarily due to the limited analgesic duration (45 to 60 minutes). In 1993 the FDA approved an oral preparation of fentanyl citrate, Oralet, that was marketed for pediatric sedation. Several studies documented the success for sedation and pain control in this population.[20-23] Though initially met with great enthusiasm, use waned and this preparation was taken off the market due to perceived financial infeasibility by the manufacturer. Fortunately, a different manufacturer released a chemically identical preparation in 2000 for the treatment of break-through pain in cancer patients. This was marketed as Actiq and several studies soon showed it usefulness in this setting.[24-27] Coincidentally, several physicians within the Special Operations community began to search for an alternative to morphine on the modern battlefield. With the advent of hypotensive resuscitation on the battlefield and subsequent decrease in IV line placement in hemodynamically stable combat trauma victims, the need for a long acting, oral analogue to morphine became obvious. In addition, Special Operations Medics and physicians had long known that the administration of morphine via the IM route was both unpredictable and often provided suboptimal pain relief.[28,7,8] Many alternatives to morphine were researched; Dr. Russ Kotwal presented oral transucosal fentanyl citrate as a possible solution. Kotwal and colleagues subsequently formulated a successful pain treatment protocol within a Special Operations Joint Task Force for the treatment of isolated extremity injuries in hemodynamically stable patients in the prehospital combat setting.[30] Following this initial trial, Wedmore et al., endorsed oral fentanyl for use in the austere wilderness setting.[31] It has now been endorsed by the Committee on Tactical Combat Casualty Care as the analgesic of choice for moderate to severe pain in combat.[32]

PHARMACOLOGY

Fentanyl is highly lipid soluble, equilibrates rapidly, and has no active metabolites. Fentanyl does not cause the release of histamine and therefore, does not cause the same degree of hypotension seen with morphine.[19] IV fentanyl does cause significant sedation and can cause respiratory depression.[33] However, IV fentanyl has a short duration of action, typically less than one hour, and generally closer to 30 minutes.[34] In typical analgesic doses, respiratory depression appears to be infrequent and very short-lived.[35]

When given in large IV bolus, fentanyl has been observed to cause chest wall rigidity necessitating chemical paralysis to ventilate the patient.[36] This is the most serious and feared side-effect of fentanyl administration, but chest wall rigidity appears to be rare at doses less than 15mcg/kg.[36] In a recent study of 841 patients given fentanyl for sedation analgesia, no episodes of chest wall rigidity were seen.[35]

Fentanyl has been extensively studied in the medical literature, and both the oral lozenge form and intravenous forms have been well documented to relieve pain with few adverse effects in both the adult and pediatric patient populations.[38-41] Intravenous fentanyl has been shown to be very effective in relieving combat trauma pain in the out of hospital setting at doses of 1 to 2mcg/kg.[42] In addition, Kotwal and colleagues found oral transmucosal fentanyl to be very effective at reducing pain in combat with only minor side-effects and only one episode of transient respiratory depression.[30]

In summary, in analgesic doses, fentanyl appears to be safe and effective for the relief of moderate to severe pain and has fewer serious side-effects than morphine.

INTRAVENOUS FENTANYL USE

The usual dosage of fentanyl for pain relief intravenously is 1mcg/kg. This dosage provides an onset of action within 30 seconds and duration of action of 20 to 40 minutes.[43] Doses larger than 2mcg/kg can cause significant respiratory depression and have been shown to cause hypoxemia and blunted response to hypercarbia in healthy volunteers.[44] Dosages of this magnitude should not be given in the out of hospital setting.

Medication errors due to fentanyl dosing in micrograms (mcg) as opposed to the more commonly used milligram (mg) dosing can cause significant dosing errors of up to 10 times the correct dose.[45] This mistake is usually due to the confusion or misreading of the dosage in-

crements, and can be catastrophic, leading to chest wall rigidity, prolonged respiratory depression, and hypotension. Extreme caution should be used to avoid this medication error, particularly in the out of hospital setting.

ORAL TRANSMUCOSAL FENTANYL CITRATE

Oral transmucosal fentanyl citrate, (OTFC) is a solid form of fentanyl citrate incorporated into a sweetened white lemon or raspberry flavored soluble matrix on a plastic handle. It is intended for oral administration over 15 minutes. Fentanyl is approximately 10 times more potent than morphine and is metabolized in the liver and intestinal mucosa by cytochrome P450 3A4 isozyme to an inactive metabolite, norfentanyl. OTFC is rapidly absorbed through the oral mucosa with the onset of action of five to ten minutes, and has terminal half life of six to seven hours. Of the total dose administered only 25% is absorbed by the oral mucosa. The rest of the medication is swallowed and undergoes significant first pass metabolism with only 1/3 of the swallowed dose reaching the systemic circulation (25% of the total). This gives a total absorbed dose of 50% of the administered preparation. The mucosal portion of the absorbed medication accounts for its rapid onset and the swallowed preparation accounts for the duration of effect. Maximum and mean serum concentration increase in a dose dependant manner.[45]

OTFC possesses a number of advantages compared with both IV fentanyl and morphine when used for analgesia. In the out-of-hospital setting, it can be rapidly administered and has a quick onset of action with prolonged duration of effect. Additionally, administration does not depend on placement of an IV or erratic absorption from IM administration.[45]

The suggested dose for oral fentanyl in the lozenge or lollipop form is 400 to 800mcg. Doses of 800mcg generally result in serum levels of 2ng/mL. In clinical trials respiratory depression has not been seen at or below this serum level.[45] A 1600mcg dosage is available, but not recommended in the out-of-hospital setting due to a significant risk of adverse effects in opiate naive individuals.[30]

SIDE-EFFECTS

Common side-effects from both IV and oral fentanyl preparations include pruritis in 50%, vomiting in 40%, and occasional transient oxygen desaturation below 94%.[31]

As previously mentioned, the most severe side-effects of respiratory depression, bradycardia, and chest wall rigidity can occur, but have not been seen in the doses recommended for use here.[36]

PRECAUTIONS

Only those trained in airway management and carrying naloxone for reversal of fentanyl's effects should use IV fentanyl in the out-of-hospital setting.

OTFC use should be closely monitored. Kotwal and colleagues suggest taping the fentanyl lollipop to the casualty's finger to allow the lozenge to fall out of the mouth should sedation occur.[30] If an attended casualty becomes sedated, removal of the lozenge from the mouth will immediately stop absorption.[45] Furthermore, it is highly recommended that any patient receiving this drug is monitored closely for any sign of respiratory compromise by both clinical and non-invasive methods (pulse oximetry, end-tidal CO_2 measurement). Likewise, naloxone should be available to medical personnel should excessive sedation and respiratory depression occur.

It should be noted that use of OTFC in opiate non-dependent patients is not approved by the FDA. Currently, the pre-hospital, combat application of this drug is considered an off-label use and every unit surgeon should take this into account when implementing a protocol for its use in his/her particular environment. The following is a recommended protocol to be used by pre-hospital extenders (Medics, Corpsmen, Special Forces medical sergeants, etc):

All providers and extenders will undergo formal training in the indications, contraindications, precautions, adverse effects, and reversal of fentanyl prior to issuance.

OTFC will be used for casualties in the austere setting when the following conditions are met:
- Rapid, narcotic analgesia is required.
- The patient must be alert and cooperative with adequate hemorrhage control.
- The patient can be monitored either directly or through the use of electronic monitoring devices.
- There are no contraindications to the use of narcotics (allergies, previous use of other narcotics or sedative-hypnotics, etc).
- The maximum dose for a single patient is 800mcg in a six hour period.
- Use must be clearly documented and related to follow-on care providers.
- Naloxone will be used per protocol for any patient with adverse side-effects due to this protocol.

CONCLUSION

Morphine and its derivatives have been used for pain control for over 3500 years. Since the Civil War, U.S. forces have used morphine derivatives for control of combat related pain with all of the inherent limitations. In modern warfare, Special Operations medical personnel have ac-

knowledged the limitations of morphine and are actively searching for alternatives. Fentanyl is perhaps the most promising alternative and appears to be uniquely suited for the management of pain in the combat setting. Fentanyl appears to be safer, more effective, and easier to use than morphine. While the available data is promising, providers must familiarize themselves with the pharmacology, dosing, side-effects, and management of complications of the use of fentanyl prior to using this alternative medication in the out-of-hospital setting. Although IV administration is probably optimal for pain control, OTFC appears to be a relatively safe and effective alternative to reduce pain in the out-of-hospital setting. Additional studies will still be required to fully understand its usefulness and adverse effects. Until then, proper understanding of this medication and precautions will need to be instituted in a protocol based fashion in order to ensure patient safety and avoidance of adverse events.

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Robert F. Kacprowicz, MD is a 1996 medical graduate from Northwestern University. He has deployed in support of OIF and OEF. He is the former Medical Director of the Pararescue and Combat Rescue Officer School, and the current Program Director for the San Antonio Uniformed Services Health Education Consortium Residency in Emergency Medicine and is a Clinical Assistant Professor of Emergency Medicine at the University of New Mexico.

Troy Johnson, MD is a 1995 medical graduate of USUHS. He is board certified in emergency medicine and has multiple deployments in support of the Global War on Terrorism. He is an Adjunct Assistant Professor in Military and Emergency Medicine at USUHS and is currently the Deputy Commander for Clinical Services at Fort Drum, NY.

Dan S. Mosely, MD is a 1996 medical graduate of USUHS. He is board certified in emergency medicine and is currently the Command Surgeon of Systems Performance Office. He is also an Adjunct Assistant Professor in Military and Emergency Medicine at USUHS and has multiple deployments in support of the Global War on Terrorism.