The Special Operations Medical Association's Official Journal

JSOM

JOURNAL *of* SPECIAL OPERATIONS MEDICINE™

Summer 2015
Volume 15, Edition 2

THE JOURNAL FOR OPERATIONAL MEDICINE AND TACTICAL CASUALTY CARE

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Dedicated to the Indomitable Spirit and Sacrifices of the SOF Medic

A Peer-Reviewed Journal that Brings Together the Global Interests of Special Operations' First Responders

Rationale for Use of Intravenous Acetaminophen in Special Operations Medicine

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ABSTRACT

Use of intravenous acetaminophen has increased recently as an opioid-sparing strategy for patients undergoing major surgery. Its characteristics and efficacy suggest that it would a useful adjunct in combat trauma medicine. This article reviews those characteristics, which include rapid onset, high peak plasma concentration, and favorable side-effect profile. Also discussed is the hepatotoxicity risk of acetaminophen in a combat trauma patient. It concludes that intravenous acetaminophen should be considered as an addition to the US Special Operations Command Tactical Trauma Protocols and supplied to medics for use in field care.

KEYWORDS: *acetaminophen, intravenous; trauma, combat; prolonged field care*

Introduction

Pain management is an important component of field combat trauma. However, effective pain management is complicated by the environment in which care of the combat casualty occurs. Combat casualty care is, by its nature, temporizing care that tries to balance competing demands and limitations. These may include exposure to austere environments; tactical or operational concerns; lack of advanced equipment; isolation from definitive tertiary medical facilities by time, distance, and/or means of travel; portability; and the skill set of combat medics and field medical teams.

An ideal pain management protocol for Special Operations medicine would provide adequate pain relief, would not affect cognitive function, would not require emergency airway management or create complications in a critically injured patient, would be simple to teach and maintain proficiency, would be sustainable for hours or days, and would be portable. Because there may never be a "perfect" agent or protocol, continued examination and revision of the protocols are prudent to improve current practice.

Special Operations trauma protocols have attempted to mitigate the problematic effects of opioid-based analgesia by adapting a multimodal approach to pain in a combat casualty. Acetaminophen has analgesic effects that act synergistically with opioids and have long been combined with oral opioids such as hydrocodone and oxycodone. Unfortunately, lack of an injectable form of acetaminophen has limited its use in clinical situations that preclude use of oral agents. However, an intravenous (IV) ready-to-use form of acetaminophen (Orfirmev®; Mallinckrodt Pharmaceuticals, www.ofirmev.com) is now available in the United States. The need to devise pain management strategies that reduce the use of opioids and other agents with cognitive side-effects suggests that IV acetaminophen should be considered for analgesia by Special Operations Combat Medics.

History

Propacetamol, an IV prodrug of acetaminophen, has been used in Europe for many years. The standard dose of propacetamol was 2g, which rapidly converted in vivo to 1g of acetaminophen.[1,2] Although never approved for use in the United States, its safety profile has been established by long-term use. Furthermore, propacetamol's rapid conversion to acetaminophen makes its tolerability profile nearly identical to that of acetaminophen.[3] Nevertheless, propacetamol would likely have had limited use in Special Operations due to lack of US Food and Drug Administration (FDA) approval and because it was manufactured in a powdered form that required reconstitution with sterile diluents that would have hindered its field use.

Recently, an injectable form of acetaminophen has been developed and subsequently has received FDA approval for the management of mild to moderate pain as monotherapy and for moderate to severe pain in conjunction with opioid analgesics. Its use is being studied in a variety of clinical situations and prospects for its increasing use in pain management suggest that it should be considered for use in combat trauma. It was also approved

by the FDA for fever reduction, a characteristic that could be incorporated into a supportive care algorithm during field treatment of infection.

Pharmacokinetics and Efficacy

Paracetamol is converted to acetaminophen in vivo by plasma esterases. The standard dose is 1g, which produces a pharmacokinetic profile similar to the oral absorption of 0.5g of acetaminophen after the first hour.[4] However, while oral acetaminophen is characterized by slow onset of action and variable analgesic activity, IV administration results in faster onset, more predictable pharmacokinetics, and reduced time to meaningful pain relief.[2,5] Peak plasma concentration occurs 15 minutes after administration, compared to about 60 minutes after oral, and 4 hours after rectal administration.[2] Additionally, IV acetaminophen avoids first-pass hepatic metabolism via portal circulation, which may reduce the potential for hepatic toxicity.[5]

The mechanism by which acetaminophen produces analgesia is not completely understood.[2] The presumed mechanism of action is selective inhibition of central prostaglandin synthesis via the cyclooxygenase pathway.[2,4] However, it has also been suggested that acetaminophen may activate descending serotonin-mediated inhibitory pain pathways as well as acting as a peripheral anti-inflammatory agent.[6] The central analgesic effects are facilitated by acetaminophen's ability to cross the blood–brain barrier.[4]

Given acetaminophen's central effects, the IV route has significant advantage over the oral route, due to earlier and higher peak cerebrospinal fluid levels.[2] In fact, IV acetaminophen results in a higher maximum plasma concentration and shorter time to maximum concentration compared with oral formulation at equivalent doses. These effects account for faster-acting analgesia and reduced time to meaningful pain control relative to the oral route.[2]

Numerous studies have established the analgesic effect of IV acetaminophen in a variety of clinical situations. The initial randomized controlled trials demonstrated efficacy of IV acetaminophen in major orthopedic surgery.[1,7] Subsequent systematic review of placebo-controlled trials for a variety of major surgeries demonstrated improved analgesia with IV acetaminophen.[8] It reduced postoperative morphine consumption after both orthopedic surgery and spinal fusion surgery.[4,6] It reduced meperidine consumption, postoperative nausea and vomiting, and time to extubation in patients admitted to the intensive care unit after major surgery.[9] One study demonstrated that 1g of IV acetaminophen produced postoperative analgesia similar to 30mg of IV ketorolac.[2]

For oral and IV routes, patients weighing at least 50kg can receive 1g every 4 to 6 hours to a maximum of 4g per 24 hours. The minimum duration between doses is 4 hours except in cases with extreme renal impairment, in which case dose frequency should be no sooner than every 6 hours. Patients weighing less than 50kg and pediatric patients are dosed based on weight at 10 to 15mg/kg to a maximum of 75mg/kg per 24 hours.[2]

Adverse Effects

The side-effect profile of acetaminophen suggests that it would be safe in combat trauma. It has not been associated with the postoperative side-effects commonly associated with opioids, including respiratory depression, sedation, nausea and vomiting, pruritus, or urinary retention.[4,6] Likewise, it does not reduce glomerular filtration rate in patients with normal renal function.[2] There is suggestion of a dose-dependent antiplatelet effect, due to weak inhibition of cyclooxygenase –1. However, this effect is transient and minor relative to the anti-platelet effect caused by nonsteroidal anti-inflammatory drugs (NSAIDs).[2]

Perhaps the greatest concern of acetaminophen administration in a patient in shock is the risk of hepatotoxicity. The majority of acetaminophen-related cases of acute liver failure are due to outpatient use in excess of the recommended daily limit of 4g.[5] At therapeutic dosing (up to 4g daily), acetaminophen is only rarely associated with hepatotoxicity, even in patients with underlying liver conditions.[5] In patients undergoing major surgery, including major orthopedic, open pelvic and open abdominal procedures, thoracic and cardiac procedures, and spine surgeries, there were no elevated liver enzyme levels in liver function test results or clinically relevant adverse effects versus control when IV acetaminophen was administered at a dosing regimen of 1g every 6 hours or 650mg every 4 hours for 5 days.[5] In another study, no changes in renal or hepatic function relative to placebo were found in orthopedic surgery patients administered the bio-equivalent of 1g IV acetaminophen every 6 hours for 24 hours.4 It should be noted that the risk of hepatotoxicity in overdose is worsened by alcohol consumption, a fact that has prompted the FDA to issue a consumer warning.[10] So long as overdose is avoided, the risk of hepatotoxicity is probably minimal and, when weighed against its benefit of not causing sedation, the risk to benefit calculation probably favors its use in combat trauma patients requiring pain control.

Although a 1g dose should have sufficient safety margin, limiting its use in cases of severe shock, would allow its evaluation in field medicine. Recalling that the US Special Operations Command Tactical Trauma Protocols (TTP) advocate for altered mental status and weak

or absent peripheral pulses as the best field indicators of shock,[11] it is reasonable to prohibit use in a pulseless, unresponsive patient. Thus, an appropriately considered trauma protocol with proper training should enable use of injectable acetaminophen without undue risk. In consideration of this concern, should this strategy be adapted by Special Operations, data collection for incidence of liver toxicity would be helpful in ensuring an educated risk-to-benefit decision is made.

Special Operations Applicability

Opioid-based analgesia, while normally the mainstay of acute pain management in critically ill or injured trauma patients, can be problematic in Special Operations medical care due to associated side-effects and complications that are worsened by the unique field situations in which care is delivered. Multimodal anesthesia, or the use of multiple agents and techniques, is a useful concept that improves analgesia while limiting opioid-related side-effects.[2] Special Operations anesthesia protocols already incorporate this philosophy by using regional anesthesia with opioid-based pain control. The addition of NSAIDs or acetaminophen to pain protocols would further this goal. Unfortunately, the risk of adverse effects such as bleeding and renal impairment limits the use of NSAIDs.[2] Oral acetaminophen is an option in the TTP as a component of the combat pill pack for wounded personnel still able to fight,[11] but its efficacy is limited in field care, due to slow onset, minimal analgesia, and the ability of a critically injured patient to ingest an oral medication.

IV acetaminophen has already been incorporated into the TTP, but only as an antipyretic option in the blood transfusion protocols.[11] As an analgesic it offers rapid onset, a favorable side-effect profile that includes lack of sedative effect and a likely low risk of hepatotoxicity for most clinical situations, synergy with opioids, and the ability to repeat doses in prolonged field care scenarios. Additionally, it probably represents the best available analgesic option for mild traumatic brain injury, a scenario in which both NSAIDs and sedating analgesics are problematic. In fact, its main limitation is probably weight, since it is formulated in bottles weighing about 4oz, which could be problematic for light infantry, given the excessive loads already carried by medics. Nevertheless, with widespread use, it is conceivable that the manufacturer could create more a concentrated formulation to address this limitation.

Conclusion

In the United States, IV acetaminophen has been used increasingly during the perioperative period for moderate to severe pain. Its characteristics including rapid onset, high peak plasma concentration, lack of hepatic first-pass metabolism, favorable side-effect profile, and demonstrated efficacy as an opioid-sparing strategy suggest that it offers enough advantages to warrant consideration as an analgesic adjunct for use by combat medics in the Special Operations and field medicine environment.

Disclosures

The author has nothing to disclose.

Disclaimers

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the US Special Operations Command, the Department of the Navy, the Department of Defense, or the US Government.

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