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Review Article

Opiates and the Development of Post-Injury Complications: a Review

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Abstract: Opiates are the analgesic of choice for the treatment of post-burn, -trauma and -surgical pain, however, it is also well-established that opiates can induce immune complications. These complications, independent of the analgesic regime, are also associated with severe traumatic injuries, such as burns. Recent findings suggest that opiates can contribute to immune and infectious complications in experimental and clinical settings. Based on the immunomodulatory properties of opiate analgesics their therapeutic use/misuse post-injury may contribute to the development of complications leading to increased morbidity and mortality in this patient population. An improved understanding of the relationship(s) between opiates and complications following major injury, such as burn trauma is likely to contribute towards an improvement in existing, as well as the development of new therapeutic regimes. This review will focus on the role of opiate analgesic usage and abuse and in the development of complications following major traumatic injury with a particular emphasis on burn injury.

Key Words: Morphine, immune, infection, macrophage T-cell, burn

Introduction

Opiate analgesics (i.e., morphine and other opiate derivatives) are the preferred treatment for the management of patient pain associated with burn injury, major trauma, surgical trauma and cancer [1-4]. Nonetheless, while these drugs have excellent analgesic efficacy, it is well-documented that chronic or therapeutic use of opiates can compromise a wide range of immune functional parameters [5-9]. In this regard, studies have shown that morphine can induce the following: immunosuppression [10-14], an immunosuppressive Th-2 cytokine profile (i.e., increased IL-4, IL-10 and/or decreased IL-2, IFN-γ) [15,16], suppressed macrophage functions [17-21], and increased susceptibility to infection [2,22,23]. Since opiates are the primary analgesic used in trauma patients, it is important to point out that these opiate-induced immune complications are also associated with major traumatic injury, such as thermal injury [24-35].

Post-burn immune complications, such as these listed above, appear to be related to the activation of a macrophage-dependent pro-inflammatory cascade [25,36]. The release of inflammatory cytokines by macrophages is an important mechanism by which they regulate the inflammatory response and aspects of both innate and acquired immunity. Macrophage hyperactivity has been implicated in the increased susceptibility to sepsis following thermal injury [37,38] and is consistent with a "two-hit" phenomenon where trauma (1st hit) "primes" the host to exhibit an abnormal response to a 2nd hit (i.e., sepsis) that is contained by a healthy host, but not a compromised host leading to the development of multiple organ failure and death [39]. Previous studies have examined cellular priming and peripheral organ dysfunction in two-hit models where the initial injury (i.e., ischemia, hemorrhage, burn) was followed by wound infection, cecal ligation and puncture, or endotoxin challenge [29,40-43].

Clinical Perspectives on Opiates and Post-Injury Complications

A recently completed retrospective clinical study on the impact of opiate analgesics on

the development of post-burn infections suggests that opiates can increase burn patient morbidity [44]. A total of 237 cases and matched controls were included in the study. Patients who developed infections were 20% more likely to be in the high opiate intake group. Interestingly, this association was modified by burn severity. Among patients with smaller burns (≤13% total body surface area, TBSA) who were in the high opiate use group were 80% more likely to develop an infection. Among patients with moderate burns (14% to 26% TBSA), the high opiate use group was 34% more likely to develop an infection and those with large burns (>26% TBSA), the high opiate use group use was similar between those who did and did not develop infections. The results of this clinical study suggest that burn patients who use large amounts of opiate analgesics are at increased risk of infection.

In support of this observation, a recent retrospective clinical study has shown that morphine for the treatment of chest pain in heart patients increases the risk of mortality [45]. These findings strongly support the concept that therapeutic opiates can adversely affect outcome following injury. Patients hospitalized for a heart attack have long been treated with morphine to relieve chest pain. In their analysis of more than 57,000 high-risk heart attack patients, approximately 30% of who had received morphine within the first 24 hours of hospitalization, they observed that those who received morphine had a 6.8% mortality rate, as compared to a 3.8% mortality rate for patients receiving nitroglycerin. The researchers found that patients who were given morphine had 48 percent higher risk of dying and 34 percent higher risk of suffering another heart attack while in the hospital. Moreover, the increase in mortality persisted even after adjustment for the patients' baseline clinical risk.

Opiates and Immune Function

Abusers of opiates have an increased incidence of infectious complications [46,47]. This observation has been confirmed in animal studies demonstrating that opiate treatment decreases resistance to infections by microbial agents [2,22,48]. Both therapeutic and chronic opiate use has a broad range of effects upon the immune system [6,9,49]. In animal models, morphine treatment has been shown to suppress immune parameters such as delayed type hypersensitivity (DTH), lymphocyte proliferation, natural killer (NK) cell cytotoxicity, antibody production, cytokine production, phagocytic function, induce lymphoid organ atrophy and diminish CD4+/CD8+ ratios [5,6,17,50-54].

Recent data suggests that activation of opiate receptors on immune cells induces altered intracellular Ca+2 levels, activation of cAMP-dependent pathways and changes in MAP kinase activation [55-59]. Morphine can negatively regulate IFN-γ promoter activity by decreasing either NF-κB signaling or MAP kinase/AP-1 signaling [56]. In contrast, others have shown that morphine sulfate can induce activation of the ERK pathway [55]. Shahabi et al., [57] have recently shown that δ-opioid receptors modulate T-cell receptor signaling through a JNK/SAPK-dependent pathway leading to activation of ATF-2. Roy et al. [60] have shown that morphine increases LPS-induced expression of IL-6 and TNF-α through the NF-κB pathway. Macrophage nitric oxide, IL-12 and TNF-α production are also enhanced by morphine under basal and LPS-activated states [14,61]. A major concern with opiates is their profound immunosuppressive properties. The opiate-induced suppression in immune function has been demonstrated at the level of T-cell proliferative responses [12,19,62], development of an immunosuppressive Th-2 profile [15,62], and decreased production of antibodies in response to antigenic stimuli [11,63]. With regard to burn injury, morphine treatment of mice with a small burn induced immune dysfunction that was not evident in untreated burned or sham animals receiving only morphine sulfate [64]. In this study mice were subjected to a small 6.25% total body surface area (TBSA) burn and treated with morphine sulfate (2 mg/kg bwt/day). Neither burn injury nor morphine treatment alone altered splenic T-cell proliferation. In contrast, morphine treatment of burned mice suppressed splenic T-cell proliferation at 4 and 7 days post-injury. The suppressed T-cell response correlated with increased nitric oxide production and expression of a Th-2 type phenotype. These findings demonstrated that mice treated with a clinically relevant dosage of morphine sulfate after an “immunologically insignificant” burn injury displayed significant immune derangements and immuno-suppression.

The mechanisms responsible for opiate-

induced alterations are not completely understood. They appear to be related to the direct action on immunocompetent cells and indirect action through the central nervous system (CNS) and the hypothalamic-pituitary adrenal (HPA) axis [65-71]. HPA activation induces ACTH production from the pituitary, and subsequent release of immuno-suppressive glucocorticoids by the adrenals. Moreover, primary and secondary lymphoid organs (i.e., spleen) have sympathetic innervations which upon activation by opiates can produce catecholamines that are also immunosuppressive [72]. In this regard, Tracey [73] has proposed an important role for sympathetic innervation in the control of the inflammatory response.

The majority of burn patients receive opiate analgesics for the treatment of pain associated with the initial injury as well as for post-injury procedures, such as wound debridement. Since opiates have profound immunomodulatory effects, it is likely that treatment of burn patients with these drugs alters their immune response to the injury. Earlier studies examined the impact of opiates on post-burn immune function [74,75]. However, these studies were directed towards understanding the potential role of endogenous opiates such as β-endorphin, rather than the impact of exogenous opiates administered to burn patients in the ICU (i.e., morphine sulfate, fentanyl, hydromorphone, meperidine). There is evidence that neuropeptides, especially the opiate receptor agonists, are involved in wound healing [76-80]. Opioid peptides have been used in animal models in treatment of wounds, as they induce fibroblast proliferation and growth of capillaries, and accelerate the maturation of granulation tissue and the epithelization of the defect. Interestingly, Poonawala et al., [81] observed that topical application of opiates accelerates wound healing by up-regulating nitric oxide synthase and the vascular endothelial-derived growth factor receptor Flk1 in the healing wounds. In contrast, however, Kramer et al., [82] have shown that the intraoperative use of morphine nerve paste might delay wound healing and increase postoperative morbidity. The impact of opiates on wound healing is unclear.

Interestingly, several studies suggest that opiates can have positive effects in brain injury, as they can modify some trauma-induced cellular events and pathologies [83-85]. More recently Zohar et al., [86] have shown that morphine administrated to mice immediately after brain injury protected them from long-term cognitive deficits. These findings suggest that activation of the endogenous opiate system may influence the pathogenesis of traumatic brain injury. Thus, whereas opiates may be detrimental in organ injury, burns and hemorrhage, they may prove to be beneficial in cases of traumatic brain injury.

Opiate Derivatives

While morphine sulfate is the most widely used opiate for pain management in adults, other types of "pure-opioids" are also employed under such conditions. They include meperidine, fentanyl, and hydromorphone. Meperidine has lower analgesic potency than morphine, whereas fentanyl and hydromorphone have greater potency than morphine. To date, only a few studies have examined the immunomodulatory properties of these non-morphine opiates [87-89]. Yeager et al., [88] demonstrated in human volunteers that fentanyl increased NK cell cytoxicity and circulating CD16+ lymphocytes. Other immune parameters, such as T-cell proliferation and neutrophil cytoxicity were unaltered. In contrast, in a murine system, fentanyl treatment of splenocytes has been shown to suppress T-cell proliferation, IL-2 production and NK cell function [87]. Meperidine had no such effect on immune function. Sacerdote et al., [89] examined the effect of a range of opiate drugs including morphine sulfate and hydromorphone in mice. They found that treatment with morphine suppressed splenic T-cell proliferation, IL-2 production and NK cell activity. In contrast, hydromorphone, while analgesic, did not alter immune parameters at any dose tested (2.5-20 mg/kg bwt). These studies suggest that different commonly used opiate drugs have different effects on immune function. Nonetheless, these studies were done in normal volunteers or animals and it remains unknown if similar responses would be observed in an injured patient.

Opiate Receptors

The pharmacological effects of opiates are mediated by several kinds of receptors. The primary receptors are the μ-, δ-, and κ-receptors [7,9,90]. These receptors belong to

the family of G-protein linked receptors and are related in structure to receptors for other neurotransmitters [90]. A wide range of second messengers and signal transduction pathways (i.e., cAMP, Ca+2, MAP kinases, NF-κB, AP-1 etc) are involved in the activation and regulation of inflammatory genes such as IL-6, TNF-α, iNOS, COX-2 [28,36,91,92].

Therapeutic opiates produce their activity by mimicking the action of endogenous opioid peptides (i.e., metenkephalin, β-endorphin, dynorphin) at receptors in the CNS, immune system and elsewhere. The three main types of opiate receptors, each with their own subtypes, are mu (μ, μ1, μ2), delta (δ, δ1, δ2) and kappa (κ, κ1-4). In vitro studies in humans and rodents support the concept that all three main types of opiate receptors can modulate immune function [93-96]. Taub et al., [96] showed that the opiate-induced suppression of murine splenic antibody responses can be mediated through either the μ- or κ-opioid receptor. Additional findings by this group have demonstrated that the δ-receptor effect is through the δ2 receptor subtype [95]. In contrast, studies by other investigators [97] suggest that the immunomodulatory effects of morphine are through the μ receptor. These studies demonstrated suppressed NK cell activity and T-cell proliferation, diminished CD4+/CD8+ ratio and lymphoid atrophy. However, these studies used either a μ receptor knockout mouse or administration of a μ receptor agonist to the left ventricle of the brain. Thus, they do not preclude a role for the other opioid receptors on peripheral immune cells. While traditionally, it is thought that a given response to an opiate results from an interaction with a single type of receptor (μ κ, δ), Smith and Lee [90] have recently proposed that interactions between receptor types play a major role in opiate action. These interactions may be local (i.e., same tissue such as immune cells) or non-local (i.e., different tissues such as CNS and immune cells). Non-local interactions would involve inter-cellular mechanisms, whereas local interactions would potentially involve both inter- and intracellular interactions. Thus, it is plausible that therapeutic opiates may exert their action on one particular receptor type in the CNS and another receptor type in the immune compartment, which both ultimately influence immune functions by differing mechanisms.

Drug Abuse and the Trauma Patient

Studies suggest that the number of burn patients reported as abusing drugs prior to admission is on the increase [98]. The patients identified as drug abusers had increased morbidity as compared to non-abusers. More recently, burn units are increasingly treating a new type of patient, individuals injured in explosions/fires from homemade laboratories producing methamphetamines [99]. One major difference in this patient population is that the patients injured in methamphetamine lab explosions are typically drug users and need to undergo withdrawal during treatment. A recent study by Santos et al., [100] indicates that increasing incidences of burn injuries are related to methamphetamine laboratory accidents. In this patient sub-population, most patients are also positive for poly-substance abuse. Specifically, all the methamphetamine patients were positive for methamphetamine and most of them had a positive screen for two or more drugs compared with the control group. The most commonly abused recreational drugs with methamphetamine were opiates, benzodiazepines, and cannabis. These patients required higher levels of resuscitation as well as sedation. In addition, methamphetamine lab patients tended to have a higher skin graft loss as compared with the graft loss rate in the control group. Future studies assessing the impact of drugs of abuse, and particularly opiates, on trauma patient morbidity are clearly warranted.

Conclusion

Traumatic injury occurs with alarming frequency in the United States. In this regard, burn injury is a significant health problem in the United States with approximately 70,000 people sustaining such injuries requiring hospitalization each year [101]. Improvements in therapeutic procedures for the treatment of burn victims have improved patient prognosis, however, high morbidity and mortality rates remain as major concerns. Some of the causative factors for post-burn morbidity and mortality may be in part related to therapeutic regimes employed in the treatment of such patients. In this regard, opiates (the analgesic of choice for the treatment of post-burn pain) can induce immune complications and increased infectious complications. Nonetheless, pain management in trauma patients is a primary concern that should take precedence over the potential immune complications that opiates might induce. In the

future, the development of novel analgesic regimes that maximize analgesic efficacy and minimize immune/infectious complications is warranted and likely to lead to decreased morbidity and mortality in this unique patient population.

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