Health Services Insights

REVIEW

Narcotics in Rheumatology

Mahsa Tehrani[1], Mathia Aguiar[2] and James D. Katz[1]

[1]Department of Rheumatology, George Washington University, Washington, DC, USA. [2]Department of Immunology and Rheumatology, Hospital General de Occidente and University of Guadalajara, Guadalajara, Mexico.
Corresponding author email: mahsa@gwmail.gwu.edu

Abstract: Patients with rheumatic conditions often suffer from related chronic pain. When first-line traditional medications such as acetaminophen and anti-inflammatory medications do not suffice, then other options are needed. The traditional medications may ultimately not provide sufficient pain relief, or alternatively, they can pose as a contraindication due to underlying hypertension, renal, and/or hepatic disease. Therefore, narcotics are an alluring alternative, which if used in a multidisciplinary and systematic approach to the patient, can prove to be quite beneficial in the lives of these patients.

Keywords: opiates, narcotics, chronic pain management, pain, rheumatology

Health Services Insights 2013:6 39–45

doi: 10.4137/HSI.S10461

This article is available from http://www.la-press.com.

Introduction

The management of chronic pain is a challenge for physicians, who, in the best interest of their patients, desire to minimize side effects from pain relieving medications and who, in the name of humanity, concurrently seek to provide as much pain relief as possible. Other than prescribing lifestyle changes, such as weight loss, physical therapy, yoga, meditation, and exercise, doctors have a limited arsenal with which to address chronic pain. Such nonpharmacologic and self-management approaches to pain are indeed important complementary modalities, which can help amplify therapeutic effects of pharmacologic aids. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly invoked as first-line medications in treating musculoskeletal pain. However, when these are ineffective or cause adverse side effects or otherwise become contraindicated, then opioid analgesics may be beneficial alternatives.[1] Indeed, there are now official guidelines available from professional societies, (such as the American Pain Society), regarding incorporation of opioids in the management of patients with chronic noncancer pain.[2]

Among the driving forces behind a renewed interest in opioids for the management of muscluloskeletal pain are the many potential adverse effects of NSAIDs. For example, conditions typically afflicting older patients such as osteoarthritis and back pain are often treated with NSAIDs. But for many reasons, this same population may be especially prone to potential adverse effects on blood pressure, renal function, the gastrointestinal tract, and the cardiovascular system.[3] For example, one recent Cochrane review concluded that NSAIDs should be used cautiously in patients with chronic inflammatory arthritis who have a history of gastrointestinal comorbidity.[4] Interestingly, topical NSAIDs have been shown to play a more benign role, compared with their orally administered counterparts. The topical route leads to less systemic concentration of the drug and, hence, to a reduction in potential side effects.[5] However, a meta-analysis of the efficacy of topical nonsteroidal anti-inflammatory drugs in osteoarthritis observed that topical NSAIDs were superior to placebo in the first 2 weeks of treatment but not the following 2 weeks (albeit less effective than oral NSAIDs).[6] Therefore, given the observed short duration of pain relief and reduced potency, alternative therapies are often sought when treating long-term pain.

Anticonvulsants and antiepileptics are alternative agents sometimes employed for the treatment of chronic pain.[7] Although these drugs may have less adverse impact on renal and gastric function, they carry an increased risk of neurological side effects as well as potential arrhythmogenic properties. Clearly, there exists a significant need for alternative modalities for the management of chronic noncancer pain.[8] This review will revisit the use and side effects of opiates for rheumatological conditions. It will not, however, address nonstandard interventions such as cannabinoids, which have been reviewed elsewhere.

Justification

Opioids have an established role in the therapeutic armamentarium for rheumatic diseases. Primarily, they are employed for short-term use or as temporizing therapy until definitive surgical intervention is achieved.[9] Recently, longer term use of these agents is gaining support in chronic degenerative conditions.[10] Properly used, opiates may improve function. For example, walking speed may improve in patients taking opiates for osteoarthritis of the knee.[11] Admittedly, in a systematic review by Papalionteous et al,[12] a small negative effect of opiates on cognitive function was noted. However, the authors cannot translate the clinical significance of such a finding, and acknowledge that this appears contradictory to other papers in their review, which found no such effect.

Furthermore, The American Geriatric Society has extensively reviewed opioid use in elderly. Their guidelines advise physicians to clearly consider opioids if patients still have daily physical limitations, moderate to severe pain, or pain-related suboptimal quality of life, and who have failed acetaminophen use.[13] This notion is further supported as per the World Health Organization recommendations.

Barriers to the Use of Opioids

The causes of underutilization of opiates by physicians in the treatment of noncancer pain are myriad, including common fears of addiction, respiratory depression, and pharmacological tolerance.[11] However, the actual risk of addiction seems to be fairly small: 3% to 18% in various reports, with an average approximate risk of 10% in those on chronic opiate therapy. In a focus

group of physicians who expressed their apprehensions regarding opiod therapy in elderly, a fear of causing harm was the most commonly cited reason. Pain subjectivity and exaggeration of the amount of pain was also a common concern. Interestingly, patient-perceived barriers included a reluctance to try opiates secondary to concern for costs, side effects, potential for addiction, as well as stigma in society associated with narcotic use.[14]

A meta-analysis assessing psychotropic medications and the risk of fracture showed that regarding opioid medications, there exists a moderate but significant increase in the risk (38%) of fractures.[15] This finding, along with the known risk of increased falls in the elderly, such as falls that may arise purely from progressive cognitive decline, is another well-established barrier to prescribing narcotics for the elderly. Perhaps periodic and consistent cognitive assessment schedules should be implemented for patients on long-term opioids. This can potentially identify and rectify new or rapid declines before they result in an incident.

Opioid-induced hyperalgesia (OIH) is another potential concern in which the patient's perception of pain worsens due to long-standing opioid use. The mechanism for this event is not entirely lucid, but a popular theory involves an accumulation of inactive opioid metabolites competitively obstructing the analgesic effects of the active metabolites on μ receptors. Another hypothesis behind the amplification of pain has to do with activation of the descending pain pathways (rostral ventromedial medulla) via enhanced concentration of neurotransmitters such as cholecystokinin and N-methyl-D-aspartate.[16] As a result of activation of these descending tracts, there is increased sensitivity to pain. Although it is difficult to tease apart opioid tolerance from OIH, there are some differences. For example, with tolerance, the location and nature of the pain remains the same. However, in OIH, the pain takes on a more generalized form, as opposed to more focal, and the intensity may be worse than the initial pain symptoms. Overall, in OIH, the patient is sensitive to even minor painful phenomenon, and the patient's threshold for pain decreases. Furthermore, other generalized neuroexcitatory symptoms, including agitation, seizures, and even delirium have been reported.[16] It is important to note that this is a relatively rare occurrence and that often an appropriate multidisciplinary approach to the patient prevents such a side effect.

Finally, it should be emphasized that research on therapeutic effectiveness of various agents in general requires valid and reliable measures of pain. Since subjective assessments are a barrier to evaluating the efficacy of various pain management modalities, researchers commonly supplement pain assessments with functional assessments.

Opioids and Functional Assessment

Tens of millions of patients are affected by some form of arthritis. Although various modalities of treatment do exist, objective assessment tools for evaluation of the efficacy of specific modalities remain crude.[11] Recently, a gait-related marker has been investigated as a potential objective assessment tool. This is because normal ambulatory mechanics are altered when patients experience pain from knee osteoarthritis (OA). A common gait adjustment in response to pain is a reduction in the speed of walking. In one study, Boyer et al[11] evaluated ambulatory mechanics in knee OA patients who were on NSAIDs versus those on opioids. Overall, both groups demonstrated improved walking speeds, suggesting noninferiority of opioids in this situation despite their lack of anti-inflammatory benefit. Although the NSAID group manifested significant improvement in knee joint mechanics, in patients with contraindications to NSAID use (that is, recent gastrointestinal bleeding, renal failure, heart failure, etc.), opiates provide a plausible alternative therapy.[17]

Nociceptive Effects of Opioids

Opioid-induced hyperalgesia (OIH) has been described as increased sensitivity to stimuli that normally provoke pain or exacerbation of pain in the absence of new tissue damage.[18] OIH has been seen to develop after prolonged exposure to opioids and is defined as a state of nociceptive sensitization.[19] Although it has been described in medical literature since 1800, the incidence is still unknown and the diagnosis remains difficult to secure. Clinically, OIH manifests as hyperesthesia or allodynia and may be accompanied by other signs of opioid toxicity (eg, myoclonus, delirium, and seizures). Commonly, patients report worsening pain despite increasing doses. Typically, the worsening pain cannot be explained by progression of the

original condition.[20] Morphine is the most common offending agent.[21] The precise molecular mechanism of OIH, while not yet understood, is generally thought to result from neuroplastic changes in the peripheral and central nervous system (CNS) that lead to sensitization of pronociceptive pathways. While there are many proposed mechanisms, those involving the central glutaminergic system, spinal dynorphins, descending facilitation, and genetics have been highlighted. Of these, the central glutaminergic system is considered the most likely possibility. Other hypotheses invoke N-methyl-D-aspartate (NMDA) receptors, inhibition of the glutamate transporter system, facilitation of calcium-regulated intracellular protein kinase C, and cross talk of neural mechanisms of pain and tolerance.[19]

It is also possible that lack of effectiveness with opioids may be more common than anticipated. Traditional interventions for OIH include opioid rotation, reduction of the administered dose, detoxification, and use of nonopioid and adjuvant analgesics.[19,21] As previously noted, a major dilemma resides in distinguishing OIH from tolerance. In addition, the clinician must be able to distinguish aggravating factors to OIH including progression of the original disease process, new interval injury, and clinical exacerbation of preexisting pain.[19]

Non-Nociceptive Effects of Opioids

There may be non-nociceptive effects of opioids on the immune system as well.[22] Opioids interact with 3 known receptors: μ, δ, and κ, which are G-protein coupled.[1] The class of opioids include alkaloids, synthetic formulations, and endogenous compounds, which occur naturally within the body. Opioids function to decrease intracellular calcium levels, ultimately resulting in reduction in presynaptic neurotransmitter release. Other than analgesic effects, opioids have been found to exert immunosuppressive effects, speculated to be caused by their molecular structure. CNS-mediated immunosuppressive effects are related to decreased natural killer cell activity along with decreased lymphocyte proliferation and interferon gamma secretion. Interestingly, opioids that do not have the capability to cross the blood-brain barrier do not exert such immunosuppressive effects.[23] The mechanisms with which opioids exert their central effects, (ie, neuroendocrine axis via sympathetic nervous system route), remain unclear.[23,24] There are also reports of peripheral immunomodulating effects of opioids, but this is a less potent effect as compared with the centrally mediated pathway.[23] For instance, it has been shown that bone marrow cells exposed to chronic opioid therapy diminish the ability for macrophage progenitor cells to proliferate upon exposure to macrophage-colony stimulating factor. Furthermore, phagocytic capabilities of macrophages are compromised as a result of chronic opioids exposure. Multiple other inhibitory effects on NK cells, T cells, and inflammatory mediators as a result of opioid exposure, have been described.[23]

So, how does this translate into clinical risk of infection and sepsis in patients who are subjected to opioid therapy? The answer is not well-established as there is only a minimal number of outcome studies. However, it is of paramount importance to note that pain itself can activate sympathetic systems, thereby contributing to hemodynamic instability in the critically ill patient. Therefore, adequate analgesia is a key focus in these patients.[23] Furthermore, in rheumatologic conditions such as rheumatoid arthritis, for example, where an overactive immune system is contributing to pain, patients perhaps may benefit from the reported immunosuppressive effects of such opiate therapy.

All opioids are not created equal, meaning some exert more immunosuppressive effects than others.[23,24] Based on the results of animal studies, it is known that morphine, methadone, codeine, and remifentanyl tend to be more immunosuppressive than buprenorphine, oxycodone, hydromorphone, and tramadol.[24] Of interest, however, is an observation that tolerance may develop against immunosuppressive effects of opioids, over time.[24] This is an area for further scientific exploration.

Specific Modalities

Weak oral opioids such as tramadol may be effective in the management of chronic pain, but the scientific evidence for their superiority relative to NSAIDs is by and large lacking.[25] This is as true for the pain related to rheumatoid arthritis as it is to pain related to osteoarthritis.[25] However, the combination therapy of tramadol-paracetamol does appear to be effective in chronic low back pain.[26]

Indeed, novel combination therapies with opioids, both weak and strong, while popular, in general have as yet to demonstrate improved function.[27]

Transdermal delivery systems for opiates are widely used. Some such agents may have a role to play in the management of osteoarthritis pain.[28] Recent studies with long-acting transdermal buprenorphine have suggested an improved quality of life in addition to pain relief in elderly patients (mean age 72.8 years) with chronic pain.[29]

Iontophoresis is another drug delivery modality whereby medications are transdermally carried into the skin by an electrical current.[30] It has been shown that if the current carries the same charge as the drug of interest, then this helps to carry the drug deep and deposit it in subcutaneous tissues.[30] Fentanyl has been the most studied opioid for iontophoresis and has been shown to reach steady state fairly quickly.[30] Another advantage is that its delivery rate can be varied accordingly.[30] Therefore, this can be of significant benefit to patients with chronic pain syndromes.

It should be noted here that in addition to the expected opiate side effects, adverse cutaneous reactions to these delivery systems are common.[31]

Opioids administered intraarticularly have been studied. Some reports show intraarticular opioids to be ineffective; others report a significant positive effect on postoperative analgesia. It may be that since the degree of postoperative pain varies from patient to patient, a concerted effort must be undertaken in order to find the optimal therapeutic regimen. Although many clinical studies have been published on the intraarticular administration of various agents, morphine is the most commonly used analgesic after major surgery.[32] And although its half life is about 2 hours, when introduced intraarticularly, its analgesic effects may last 24 hours.

Another agent, methadone, is a synthetic long-acting anesthetic agent with high activity on opioid receptors and a half-life of about 35 hours. It is highly bound to plasma protein. After intra-articular injection of methadone, analgesic effects last for 24 hours. Pethidine is an anesthetic opioid drug whose half-life is about 4 hours. It has lower affinity to proteins and higher risk of convulsions than morphine. After intraarticular injection of pethidine, the duration of anesthetic effect lasts about 12 hours.[33] Tramadol is a weak (selective l receptor) opioid agonist. An intraarticular admixture of tramadol with bupivacaine provides a pronounced prolongation postoperative analgesia in patients undergoing arthroscopic knee surgery.[34] Some studies have demonstrated that the intraarticular injection of bupivacain/fentanyl is also effective, especially so in the presence of synovitis.[35] Finally, some researchers have suggested that intraarticular administration of sufentanil alone or in combination with methylprednisolone after knee meniscectomy is effective, reliable, and well tolerated.[32]

In summary, although a systematic review by Gupta et al concluded that when compared with placebo, intraarticular morphine does provide analgesic effects,[36] there exists wide variability both between and within studies regarding the intensity of analgesic properties.[36] Hence, it is difficult to extrapolate a dose-dependent analgesic effect. Therefore, creating dosing guidelines remains challenging.[36]

Other novel administration routes

The intranasal route of administration seems to be promising in multiple situations. For example, it can be ideal in the preoperative setting as well as for pain control in the postoperative time period.[30] It can be useful in the pediatric population (eg, in the setting of the emergency room) after trauma.[30] In this situation, the intranasal form works as well as the intramuscular form and is more acceptable to parents and their children.[30]

Conclusions

Overall, there are a wide variety of pain-relieving modalities in the toolbox of rheumatologists, although these agents fall within several broad categories: anti-inflammatories, acetaminophen-based agents, narcotics, numbing anesthetics, and newer experimental agents. Each category has its pluses and minuses. In the setting of addressing the needs of rheumatologic patients, recognizing each patient's unique requirements is key. In the setting of cardiovascular, gastrointestinal, or renal disease, low dose opiate therapy is well justified, and has been shown to be efficacious, even in the older patient. With proper counseling, a multidisciplinary approach, and frequent follow-up evaluations, opiates may be

a viable option in the patient with musculoskeletal pain.

Author Contributions

Conceived and designed the experiements: JDK. Analyzed the data: JKD, MT, MA. Wrote the first draft of the manuscript: JDK, MT, MA. Contributed to the writing of the manuscript: JDK, MT, MA. Agree with manuscript results and conclusions: JDK, MT, MA. Jointly developed the structure and arguments for the paper: JDK. Made critical revisions and approved final version: JDK, MT, MA. All authors reviewed and approved of the final manuscript.

Funding

Author(s) disclose no funding sources.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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