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MOLECULAR ASPECTS OF TOXICITY OF CENTRALLY ACTING ANALGESICS: A MINI REVIEW

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ABSTRACT

Pain of multiple etiologies remains a significant problem for many patients presenting in the clinical setting. Improved pain relief can be maximized and adverse effects minimized, by multimodal analgesic combinations as the method to improve pain treatment. Significant suggestion supports the use of combination analgesics for the management of pain and in some cases, they have a heterogeneous pharmacologic sparing effect. Fixed-dose combination analgesics having significant efficacy and safety are extensively suitable for pain management and are usually recommended. However, further exploration is required for the best combination that which analgesics at which doses can be pooled with a co-analgesic in a patient-specific manner to attain additive, if not synergistic, multimodal pain relief with the least possible adverse values. Unsupervised intake of over-the-counter drugs offers clinical challenges to both the patient and health care providers. Couple this often unrevealed over-the-counter medication consumption event with prescription medications, which many have similar combination constituents and the potential for a therapeutic misadventure may precipitate. Patient-specific cautions are presented for opiate/opioid combinations, codeine, hydrocodone, oxycodone and propoxyphene and there is a discussion of COX I/COX II agents. This review article address the safety and efficacy of different analgesics individually and in combination with currently available prescription dosage forms with a focus on pharmacology, pharmacotherapeutics, pharmacodynamics, and pharmacokinetics, including drug interactions and toxicity profile.

KEYWORDS: Pain, Analgesics, multimodal analgesics, toxicology, drug interactions.

INTRODUCTION

Pain is defined as one of the uncomfortable and uneasiness feeling associated with defense mechanism of the body.[1] According to World Health Organization, pain is considered as one of the most underestimated healthcare problems in the world and that opioid analgesics are effective and cost-effective pain relievers. The sensation of pain is an indication that something is wrong somewhere in the body. Pain in its real sense has no precise definition, but in general term, occurs whenever the body tissue is damaged.[2] The damage may be superficial or deep right in the tissue of the body. The function of pain is to draw attention to injury and through the reflexes elicited to protect the injured part. Whenever pain sets in, the individual reacts to remove the pain. Pain receptors and afferent pain fibers are distributed all-round the body. The pain sensation is initiated by peripheral receptors by stimuli: Such as mechanical, thermal, electrical, chemical, etc., at a threshold sufficient to cause tissue damage.[3] The pain stimulus is processed in the brain which then sends impulses down the spinal cord and through appropriate nerve which commands the body to react, for instance by withdrawing the hand from a very hot object.[4]

Global prevalence of lower back pain, for example, is estimated at 30%-40% of adults worldwide at any given time.[5] Moreover, about 50% of patients with cancer at all stages of the disease experience pain.[6] In short, there is an urgent and international need to find better ways to manage all types of pain and to raise awareness about analgesic options in the international medical community. Despite globalization, high-speed communications and increasingly open academic borders, the practice of medicine remains largely regional.[7] Many people, including Pain is often undertreated and pain management greatly misunderstood. Seventy-three percent of hospitalized medical patients receiving opiates were found in severe or moderate distress despite their analgesic regimen.[8] Caregivers' misconceptions regarding opiate doses, duration of analgesic effect and fear of addiction were partly responsible for this under treatment. Similar problems have been reported in ambulatory patients. Different management techniques are utilized for acute and chronic pain.[9] Guidelines for pain management recommend a stepped approach with consideration for the type of pain and response to therapy.[10] Initial therapy should include nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs). For mild to moderate pain, oral combinations of acetaminophen and NSAIDs with opioids are recommended.[11]

For moderate to severe pain, opioid analgesics are the mainstay. Titration of dose and frequency should be individualized to the patient's response and experience of side effects. Approximately 75% of patients with advanced cancer and 33–50% of those undergoing treatment have pain.[12] Pain is typically experienced constantly at some level in these patients and is usually managed with a fixed-schedule opioid, nonopioid, or combination regimen. However, despite being on a fixed, regular pain regimen, 40 –90% of patients experience episodic periods or flares of pain above their baseline.[13] This pain that occurs despite the standing medication regimen is termed breakthrough pain. Breakthrough pain occurs frequently in many patients and is concerning because it indicates incompletely controlled pain.[14] It coincides with patients' reporting greater underlying pain and about half of patients surveyed in one study reported an episode of breakthrough pain in the previous day.[15] The impact of this breakthrough pain is significant because it is responsible for greater functional deterioration, poor mood and increased anxiety.[16] Episodes of breakthrough pain occur around four to six times per day, have a rapid onset with peak intensity in 3 minutes, are moderate to severe in intensity and usually last less than 30 minutes, with 90% lasting less than 1 hour. It has been reported that 75% of breakthrough pain episodes last less than 30 minutes and 56% were unpredictable.[17] The characteristics of breakthrough pain make it difficult to treat with traditional oral pain medications because their onset time is often longer than the duration of the pain itself.[18] Breakthrough pain is not always unanticipated, with 55– 60% of patients able to identify the source. The most common causes were movement (20.4%) and pain before the next dose (13.2%). These studies confirm that a rapid acting rescue agent is necessary because 40% of breakthrough pain episodes are unpredictable.[19] Currently, available oral medications are not optimal agents for many breakthrough pain instances because they are slow to act and produce a number of undesirable effects, including respiratory depression, pruritus, spasm of the gastrointestinal smooth muscle and nausea and vomiting.[20] The goal of balanced analgesia is to decrease the total amount of opioids administered and in turn, produce fewer negative side effects.[21] The addition of nonopioid analgesics, specifically acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), is an important component of balanced analgesia.[22] The goal of this review is to focus on rapid-acting opioid and nonopioid agents currently available or still being investigated to treat breakthrough pain.

ANALGESIC CLASSES

TRADITIONAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs are among the most widely used medications. Given their efficacy in managing fever, mild to moderate pain and, at higher doses, inflammation, such widespread use is generally appropriate.[23] Numerous prescription NSAIDs are available, but aspirin and ibuprofen are two non-prescription NSAIDs that contribute significantly to the use of this class of medications. It has been estimated that 20–30% of Americans use an NSAID each year and 1–2% use NSAIDs every day.[24]

The generally accepted mechanism of action of NSAIDs is that they attenuate prostaglandin synthesis by inhibiting cyclooxygenase (COX) enzymes[25], although some central action has been reported.[26] NSAID side-effects, however, are often related to COX inhibition, which greatly limits their use.[27] The side-effects are primarily gastrointestinal, hematological and renal. NSAIDs cause a localized irritation of the gastric mucosa.[28] Higher doses or prolonged use may cause serious erosive gastritis and gastric hemorrhage due to a decrease in the amount of prostaglandins PGE_2 and PGI_2.[29] Risk factors for developing gastropathy from NSAID use include a history of peptic ulcer disease or gastric bleeding, continued use of alcohol and increasing age.[30] The hematological effects of NSAIDs result from their inhibition of platelet aggregation. Because of this effect, all NSAIDs need to be used with caution in patients at risk for GI bleeding.[31] Nephrotoxicity from NSAIDs is rare in healthy patients because both renal blood flow and glomerular filtration do not depend on prostaglandin levels, but the risk of nephrotoxicity increases for patients who are volume depleted, who have congestive heart failure, or who have hepatic cirrhosis.[32] Serious idiosyncratic reactions to NSAIDs that are not related to prostaglandin inhibition are rare.[33]

COX-2 NSAIDs

COX-2–selective NSAIDs have recently received much attention from clinicians, scientists, patients and the media. As their name suggests, these agents are selective for the COX-2 enzyme, which is thought to be responsible more for pain and inflammation, whereas the COX-1 isoform more commonly provides homeostasis in the intestines, kidneys and elsewhere.[34] As a result, COX-2 NSAIDs are less likely to cause gastric ulceration, but they may inhibit healing of previous ulcers and therefore should not be used in patients with a history of GI ulcers, particularly NSAID-induced ulcers.[35]

Acetaminophen

Acetaminophen (paracetamol) has been a mainstay for pain relief and fever control since its approval for use as an analgesic in 1960. Even though acetaminophen has been available for several decades, the mechanism of action by which it elevates the pain threshold is not understood.[36] The experimental evidence converges on two possibilities: an effect at the local site of injury (peripheral action) and an effect at some level, spinal or supraspinal, of the central nervous system (central action). The peripheral action would presumably be related to inhibitory modulation of peripheral mediators of pain. Some suggestions include inhibition of nitric oxide synthase, reversal of the hyperalgesia induced by NMDA (*N*-methyl-D-aspartate) or substance P[37] decrease of spinal PGE_2 release or an effect on spinal cord 5-hydroxytryptamine (5-HT; serotonin). The latter effect would have to be indirect, as we found that acetaminophen does not inhibit constitutive or inducible nitric oxide synthase (unpublished data) or bind to known 5-HT receptors or to 5-HT neuronal reuptake sites.[38] Part of the problem in elucidating the mechanism of acetaminophen may be due to the approaches taken, which have largely focused on a single pathway or site of action. In contrast to these approaches, our recent work has been directed toward dual site studies. This approach has led to the discoveries of three new properties of the mechanism of acetaminophen: (i) marked 'self-synergy' that results from spinal-supraspinal administration, (ii) the contribution of a descending endogenous opioid component and (iii) pronounced and surprising synergy with phentolamine.[39]

The side-effects of therapeutic use of acetaminophen are minimal. Unlike NSAIDs, it does not significantly inhibit prostaglandins and hence does not produce GI irritation or inhibit platelet aggregation. A serious adverse effect is hepatotoxicity, which can occur with large doses (10–15 g), when glutathione stores are depleted and a toxic metabolite of acetaminophen is allowed to accumulate.[40] Unwitting use of multiple acetaminophen preparations simultaneously can cause accidental overdose. Hepatotoxicity typically does not occur in therapeutic doses (≤4 g/day), but alcohol intoxication has been shown to predispose patients to hepatotoxicity at normal acetaminophen doses.[41]

Opioids

The use of opium, opiate extracts (e.g. morphine and codeine) and opiate-like substances (opioids) originated more than 1000 years ago and morphine was synthesized almost 200 years ago. Opioids are the most powerful pain relievers, and therefore traditional opioid

analgesics remain the drug of choice for the medical treatment of severe acute pain syndromes and for progressive severe chronic illnesses.[42]

An understanding of the mechanism of action of opioids has only become possible since the identification of endogenous opioid-like peptides and receptors in the early 1970s. Three major structurally and pharmacologically distinct opiate receptor types (μ, δ and κ) and their subtypes are located throughout the body, both in the central and peripheral nervous system. Analgesia is thought to primarily involve opioid receptors in the brain and spinal cord.[43] The most common side-effects seen with opioid therapy are constipation, nausea, vomiting, sedation, itching and respiratory depression.[44] Although most adverse effects occur at a higher dose than is required for analgesia, some effects, such as constipation, commonly occur at therapeutic doses. Tolerance and physical dependence may also occur when using opioids over long periods of time (more than 2–3 weeks of continuous administration). Fortunately, many of these unwanted effects can be treated or prevented while maintaining adequate analgesia for the patient.[45] Unfortunately, because of misunderstandings or unfounded apprehension about the possibility of tolerance or physical dependence, addiction, fear of professional or regulatory censure, or litigation, physicians are frequently reluctant to prescribe these important drugs in sufficient doses to relieve pain.[46]

Tramadol

Just as acetaminophen shares some, but not all, the characteristics of NSAIDs, tramadol shares some, but not all, the characteristics of opioids. Tramadol was initially described as a traditional opioid and has low affinity for μ-opioid receptors, more akin to the non-opioid imipramine than the opioid codeine.[47] The M1 metabolite of tramadol binds μ-opioid receptors more strongly than the parent drug, and an opioid component contributes to tramadol-induced antinociception (animals) and analgesia (humans). However, because the opioid antagonist naloxone does not reverse all of the antinociceptive or analgesic effects of tramadol, additional mechanisms must contribute significantly to its analgesic effects. Several studies have shown that tramadol inhibits re-uptake of serotonin and norepinephrine[48], which synergistically enhances the opioid mechanism of action. This binary mechanism of action may explain the reduced incidences of abuse tramadol is a non-scheduled drug), respiratory depression and other adverse opioid effects relative to traditional opioids. It may also explain why tramadol is effective in opioid-resistant chronic pain states and other painful conditions.[49]

Adjunctive therapies

In the past few years, knowledge of the neurophysiology, biochemistry and modulation of pain transmission has expanded at an increasing rate. Recently, numerous compounds have been studied to identify novel analgesic properties, including antidepressants, anticonvulsants and clonidine.[50] Because current therapy for pain relief is inadequate for some patients and chronic pain is difficult to treat, the search for new analgesic compounds or therapies will continue.

COMBINATION ANALGESICS

The combination of two analgesic drugs has the potential to overcome tolerability, efficacy and time-to-onset limitations of the component drugs and, in certain cases, synergistically to increase their analgesic effect. Combining analgesics with different mechanisms or sites of action, for example, can allow for reduced doses of the component drugs, reducing overall adverse effects with comparable analgesia.[51] Likewise, combining short-acting and long-acting agents can result in both shorter onset and longer duration of analgesia.[52]

The advantages of combining analgesic drugs has been recognized for almost a century, although until recently the experimental evidence has been lacking or inadequate, mainly due to limitations in study design and the ongoing difficulty in accurately assessing pain. Measuring synergistic interactions between drugs has also been difficult, particularly as incremental reductions in pain are not readily measurable, although models such as the isobologram are useful for analyzing a range of combination ratios over which synergy occurs. New statistical analyses and pharmacological modelling techniques, however, are becoming available.[53] These analytical methods are crucial for accurately comparing the efficacy of an analgesic combination with that of each individual agent. It is important that these evaluations be made. For example, many well-known analgesic combinations have never undergone preclinical or clinical scrutiny for evidence of statistically enhanced analgesia or reduced adverse effects at the doses or dose ratios used clinically. For chronic administration it is also important to know the relative pharmacokinetic disposition of the constituent drugs. Repeat dosing of a combination might lead to a build-up of an agent beyond the beneficial dose ratio or even into toxic ranges.[54]

Numerous clinical studies of oral analgesics have documented the benefits of combining analgesics, however, the adverse effect profile of high-dose aspirin reduces its usefulness in combination therapy and so increasing emphasis has been placed on acetaminophen

combinations.[55] Adding a NSAID to acetaminophen has been shown to improve efficacy in acute pain states; however, the additional benefit of this combination must be weighed against the increased toxicities possible with long-term NSAID use.[56] A recent trial in pediatric patients reported that there is no evidence to support combining these two drugs.[57] Although combining acetaminophen with a COX-2 NSAID may be relatively safe for long-term use, the efficacy of this combination has not yet been studied.

Only one oral NSAID–opioid combination (ibuprofen/hydrocodone) that has been shown to be effective is currently approved for use in the US. However, the combination of an NSAID with other opioids has been shown to be effective in dental pain (ibuprofen/oxycodone)[58], postoperative pain (ibuprofen/codeine), osteoarthritic pain (any NSAID with oxycodone)[59] and other forms of pain. Long-term toxicities of both NSAIDs and opioids suggest that these combinations are best suited for acute pain states, although combining an opioid with a COX-2 NSAID may partially address this concern.[60] However, no studies of such combinations are yet available and the only commercially available combination, ibuprofen/hydrocodone, is not indicated for chronic pain management.

Based on extensive evidence of their efficacy, opioid–acetaminophen combinations are recommended in the WHO analgesic ladder for moderate to severe forms of pain. In 1999, nine of the top 200 drugs prescribed (including generics) in the United States were combinations of an opioid (hydrocodone, codeine, propoxyphene or oxycodone) and acetaminophen.[61] Interestingly, clinical use of such combinations for some post- operative pain often involves the use of doses of the components that individually produce effective analgesia, yielding relatively modest gains in analgesic efficacy without significant decrease in adverse effects. For example, a meta-analysis published in this journal[62] of the use of acetaminophen combination with codeine for postoperative pain (e.g. dental surgery, episiotomy and uterine cramp), reported that evidence for some superiority of the combinations over paracetamol was obtained, but the effects were weak and probably not clinically significant.' It might be an alternative strategy in such situations to use (lower) doses, which combined produce the same level of analgesia elicited by each component, but with fewer adverse effects. This example also highlights again the importance of establishing, by rigorous preclinical and clinical evaluation, whether the combination is additive or synergistic, the optimal dose ratio and the adverse effect profile of the combination compared to the individual constituents.

Tramadol offers potential advantages over traditional opioids in combination therapy because its unique mechanism contributes to its favorable chronic safety profile, particularly with respect to respiratory depression, constipation, sedation, tolerance or dependence. Combining tramadol with acetaminophen provides a good example of the potential benefits of combination therapy. Each component has a unique analgesic mechanism of action and it has been demonstrated that adding acetaminophen to tramadol results in synergistic analgesia in animals.[63] It has been further demonstrated in humans that the combination is more effective and has a faster onset and longer duration of action than either component alone, without increasing the incidence of adverse events. Adding certain NSAIDs to tramadol may also result in synergistic antinociception. Tramadol use was shown to reduce NSAID (naproxen) doses in patients with osteoarthritis and the combination of tramadol and flurbiprofen was shown to be more effective than either agent alone for pain following dental surgery.[64] No tramadol/NSAID combinations are commercially available, but additional studies of such combinations (particularly with COX-2 NSAIDs) are needed.

CONCLUSIONS

Many combination analgesics are available and are commonly prescribed for pain. The goal is to facilitate patient compliance, simplify prescribing and improve efficacy without increasing adverse effects. Clinical trials have recently begun to document the efficacy and tolerability of combination analgesics, but additional study of these and other combinations (such as acetaminophen or a NSAID with an opioid or tramadol) are clearly needed. In special cases, the combination of drugs from different analgesic classes results in synergistic analgesia, but not synergistic adverse effects, enabling the patient to achieve increased pain control or comparable control with a lower risk for adverse events.

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