Review Article

Opioid combination: rationale and possible clinical applications

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Abstract: The aim of this review is to provide a potential benefit of an opioid combination at receptor sites, based on experimental data and preliminary clinical studies where a combination of opioids with different characteristics yielded greater analgesic activity with lesser adverse effects. The receptor activity, including intrinsic activity, endocytosis, and oligomerization, and the interaction on opioid receptors and between different opioid receptors or different sites are described. Finally, clinical observations of opioid combinations reported in literature regarding the possible benefits of such an approach are presented.

Keywords: Opioid combination; cancer pain; chronic pain; tolerance; opioid receptor

Submitted Sep 03, 2013. Accepted for publication Sep 17, 2013.
doi: 10.3978/j.issn.2224-5820.2013.09.04
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Opioids are the mainstay of chronic cancer management and are used for the treatment of moderate to severe pain. The analgesic responses to analgesics, including opioids, depend on a multitude of factors characterized by a large intraindividual and interindividual variability (1). Drug-related and patient-related factors are the most relevant. Long-term clinical use of opioids (mainly μ agonists) can cause a wide range of adverse effects such as respiratory depression, constipation, and tolerance. Tolerance to different opioid effects develops at varying rates and accrues gradually with repeated dosing. Antinociceptive tolerance is well documented and is characterized by a marked reduction in the pain-relieving effects of an opioid after repeated administration. Tolerance leads to dose escalation with the potential to increase intrinsic opioid toxicity, including opioid-induced hyperalgesia, which limits the tolerability of an opioid treatment.

It has long been appreciated by clinicians that individual patients may respond better to one μ-opioid than another, improving tolerability and restoring satisfactory pain relief. These findings suggest between-opioid differences, indicating a far more complex pharmacology for opioid receptors than it has previously been suggested (2). Pharmacological differences among μ opioid drugs have been observed *in vitro* and *in vivo* preclinical models, implying that all μ opioids may not be working through the same mechanism of action (3). Many observations suggest the presence of functional interactions among μ opioid analgesics, consistent with the involvement of multiple subpopulations of μ opioid receptors (4). Interactions with other opioid receptors have also been recently reported. It has been shown in animal studies that when a μ-receptor agonist (i.e., morphine) is co-administered with a δ-receptor antagonist (i.e., naltrindole), then increased analgesia results with an improved side-effect profile. Collectively, these data indicate the potential of synergic effects when using opioids with different receptor characteristics (5). Finally, potent interactions between selected combinations of opioids and NSAIDs have been demonstrated (6).

The aim of this review is first to provide a potential benefit of an opioid combination at receptor sites, based on experimental data and research suggesting possible clinical implications. Secondly, to provide information about preliminary clinical studies where a combination of opioids with different characteristics yielded greater analgesic activity with lesser adverse effects.

Opioid receptor activity

Opioids act through more than one μ-receptors. Opioid

receptors are currently classified as μ, δ, and κ, with a fourth related non-classical opioid receptor for nociceptin/orphanin FQ. Opioids have overlapping selectivities at μ, δ, and κ receptors as well as overlapping distribution patterns in the nervous system and differentially modulate a broad range of physiological functions (7). Opioids are commonly classified by their selectivity and affinity in receptor binding studies. Opioid receptors belong to the large superfamily of G-protein-coupled receptors. Opioid receptors act via G-proteins to inhibit adenyl-cyclase, increase potassium currents, inhibit calcium channel activity, modulate inositol triphosphate turnover, and activate mitogen-activated protein kinase. These actions culminate in the attenuation of neuronal activity by inhibiting neurotransmitter release and changing neuronal excitability. However, despite apparent similarities, many μ-opioid analgesics have interesting pharmacological differences. μ-opioids are the most common drugs used for analgesic purposes, and morphine is prototype of this class of drugs. Most genes are composed by multiple exons that must be spliced together to generate the mRNA that in turn produces the μ-receptor. Variability or mutation of these sequences may provide the ability of a single gene to generate a wide range or related proteins (8). The regulation of the splicing is even more complex, dependent on the cell (for example, spinal cord or other sites), and localization (for example pre or post-synaptically) (9).

The binding pocket of these variants, however, is identical, showing high affinity and selectivity for μ-opioids. However, the number of receptors needed to be activated in order to suppress neuronal activity differs significantly. Receptor conformation changes as a result of opioid binding and subsequently determines the efficacy of receptor activation and G-protein interactions.

Intrinsic activity

Receptor occupancy and drug effect are directly related to the number of spare receptors. According to the law of mass action, more potent drugs modify relatively fewer receptor-effector mechanisms to produce an effect. It has been suggested that the degree of tolerance is inversely related to the reserve of spare opioid receptors (10). Different drugs may produce equivalent pain relief while occupying different proportions of the available receptors (i.e., having different fractional receptor occupancies). As morphine has high occupancy characteristics, it is considered a low intrinsic efficacy agonist, and may induce tolerance more readily than a high efficacy agonist (11). Fentanyl, methadone, and etomorphine showed a greater receptor reserve than do morphine, levorphanol, and meperidine (12,13). Thus, the extent of tolerance to the analgesic effects of μ-opioid agonists has been found to vary with the intrinsic activities of both of drug used to induce the tolerance and the drug being tested for analgesic activity (12). The latter hypothesis also has been tested in relation to the dose-response changes with progressive increases in stimulus intensity (14,15). Several opioids, including methadone, fentanyl and sufentanil have been demonstrated to have much higher efficacy than morphine, due to a higher receptor reserve than morphine (10,16), possibly also due to their greater ability to induce receptor internalization. When acting through the same receptor, morphine, with its lower reserve, may lose its effectiveness as a result of tolerance, acting as a partial agonist when compared to methadone (17).

With an increase in stimulus intensity, opioids with a high efficacy showed less shift in their dose response curves than an agonist with low efficacy (like morphine), that shows a greater reduction in the maximum effect and increased occupancy requirements. The greater shift in morphine dose-response relative to sufentanil when stimulus intensity rises may support the receptor occupancy theory. Thus, whereas morphine acts as a full agonist at low stimulus intensity, it may become a partial agonist at high levels of pain stimulation, and the relative potency of sufentanil to morphine increases as tolerance develops (14). Although significant cross-tolerance for both sufentanil and morphine has been demonstrated, the magnitude of cross-tolerance from sufentanil to morphine was greater than from morphine to sufentanil, showing an asymmetrical cross-tolerance (17). The level of antinociception produced by an opioid seems to be dependent on the intrinsic efficacy of the drug and the stimulus intensity. Interestingly, the level of antinociception produce by an opioid "per se" and not necessarily the opioid intrinsic efficacy, may determines the type of interaction among opioids (18).

Endocytosis

Endocytosis has a well-established role in the desensitization and downregulation of receptor-mediated signaling, both of which have been implicated in the development of tolerance. The ability of selected opioid analgesics to mediate regulation of receptor signaling by rapid endocytosis represents an independent functional property that distinguishes clinically important opioid analgesics such

as morphine and methadone. Following activation, opioid receptors are regulated by multiple mechanisms, including a well-characterized and highly conserved process involving receptor phosphorylation by G-protein coupled receptor kinase a subsequent arrestin recruitment. These processes can contribute to desensitization by facilitating the uncoupling of receptor from G protein. Following this desensitization, receptors are often endocytosed into an intracellular compartment, from which they can be recycled to the membrane, leading to receptor downregulation. According to this theory endocytosis serves a protective role in reducing the development of tolerance. This property profoundly affects the regulation of downstream signaling and can be distinguished both pharmacologically and mutationally from other important functional parameters such as potency and intrinsic activity for receptor activation. The downstream regulatory responses induced by the failure of morphine to promote efficient arrestin-mediated desensitization may include additional modifications of the receptor itself that change the apparent functional receptor reserve independent from changes in total receptor number (19).

Oligomerization

Receptors are coupled with a G-protein composed of three units. When the complex is activated, GDP in the complex unit of G-protein is replaced by GTP and leads to the transduction of the signal. The receptor associated with G-protein is tightly complexed by a number of proteins, producing a larger size of the solubilized μ-receptor complex (7). The ability of the receptors to dimerize and their association with G-proteins, due to the different variants, define the type of transduction and the response. Thus, dimerization is a means by which G protein can cross talk and amplify signals (20). Studies have confirmed that opioid receptors not only dimerized in various combinations but mostly exist as receptor dimers and not monomers in different tissues. Dimerization may modulate receptor function (21). Heterotypic dimers have different opioid binding affinities, intrinsic efficacy, and receptor trafficking than monomers. In this way, different receptors, localized in different places, centrally or peripherally, all bind the same drugs, but may produce a different effect, leading to either positive or negatively cooperativity (7).

Interactions on μ-receptors

The μ-opioid system is extremely complicated. The actions of a μ-opioid reflect the summation of the activation of all the μ-opioid receptor. Although the μ-opioids generally show similar binding affinities for most of the different opioid receptor variants, their ability to activate the various receptor subtypes differs. The pharmacological effect of each splice variant may vary from drug to drug depending upon its potency and efficacy at that particular site (3). Opioid receptors undergo adaptations such as desensitization, down-regulation, and internalization in response to repeated administration of an agonist, each of these phenomena contributing to the development of tolerance that undermines the use of opioids as analgesics (22).

Opioid receptors are endocytosed by a mechanism involving receptor phosphorilation, interaction with β-arrestin and then sequestered internally. Trafficking of G-protein-coupled receptor by rapid recycling pathway restores the complement of functional receptor and process resensitization of receptor mediated signal transduction (23).

The regulation of opioid receptors by endocytosis has been hypothesized to have protective functions in reducing the development of tolerance. Agonist activity and receptor endocytosis have opposing effects on receptor-mediated signalling, and the final result is a function of both processes (named RAVE). Morphine, in comparison with other opioids has a high activity-endocytosis ratio, and has an enhanced propensity to prolonging signals with prolonged drug exposure (24). The amount of internalization caused by an agonist generally correlates with coupling efficiency.

Molecular events, such as desensitization and endocytosis would reduce this response. It has been experimentally demonstrated that endocytosis-promoting agonists may facilitate morphine-induced receptor endocytosis, reducing the compensatory adaptive cellular changes that lead to upregulation of the cAMP pathway (25). Coadministration of DAMGO or fentanyl promoted morphine-induced μ-receptor internalization. The analgesic effect of morphine was greatly potentiated when μ-receptor internalization was induced by coadministration of subanalgesic doses of DAMGO or fentanyl. In contrast, the combination of DAMGO and fentanyl increased neither the analgesic effect not the internalization of μ-receptor (26). Thus, a combination of opioids with different characteristics may reciprocally alter their RAVEs, so reducing the potential for the development of tolerance. On the other hand, morphine treatment can produce adaptational changes which can attenuate high efficacy agonist-mediated desensitization and internalization of G-protein-coupled receptors (27).

Functional interactions among μ opioid analgesics have

been demonstrated. Synergy between methadone and a number of other μ-opioids have been found, also revealing incomplete cross-tolerance (28). The combination of methadone with morphine offers a number of potential advantages, particularly since these interactions seem to be restricted to analgesia, as inhibition of gastrointestinal transit is not increased. Moreover this effect was not attributed to an interaction with NMDA receptors (4). Not all μ-analgesics have revealed synergy when given in combination. Only additive interactions between methadone and fentanyl or between morphine and M6G, have been found.

Interactions between different opioid receptors or different sites

Synergy is a commonplace in opioid pharmacology. The interactions between opioid receptors have been the subject of recent research. It has been postulated existence of functional interactions between opioid receptors (29). It has been shown for morphine given both supraspinally and spinally underlining the importance of regional interactions either between different places in CNS and/or periphery (30,31), the route of administration having *per se* an effect on the degree of synergy (28,32). In animals rendered tolerant to systemic morphine, a lack of tolerance to intracerebrally administered morphine was found. Similarly highly lipophilic μ-agonists, for example methadone given peripherally, show no analgesic cross tolerance in animals treated by morphine, suggesting that changes in the ability to cross the blood-brain barrier or other dispositional changes may be involved in the differential tolerance development (33).

The fact that opioids can act with multiple receptor activities and with site-dependent receptor profiles has encouraged research to explore the interactions among different receptors. Although each opioid receptor can mediate its effect independently, a growing body of evidence has been accumulating for the existence of cellular or molecular interaction among opioid receptor types. In an early study alternating μ and δ receptor activations modified the development of tolerance (34). Although the stimulation of μ, δ, and κ-receptors produces distinct pharmacological effects, a possible co-localization in the same synapse may cause a substantial interaction between them, or a combination of effects on different receptors result in a synergic effect. Synergy has been demonstrated between μ and δ opioids (35,36). There is some experimental evidence to suggest that blocking δ-receptor while activating μ produces antinociception without the development of tolerance (5).

Functional interactions among opioid receptor types, not always bidirectional, have been demonstrated. The repeated stimulation of κ-opioid receptor markedly increased the functional μ and δ-opioid receptor, whereas repeated stimulation of either μ- and δ-receptor had no direct effect on κ-opioidergic function in mice (37).

Morphine and oxycodone appear to exert their antinociceptive actions via different classes of opioid receptors (24,28,38,39). In contrast to morphine, intrinsic antinociceptive effects of oxycodone seem to be principally mediated by putative κ-receptors (40). These findings could explain the asymmetric tolerance existing between oxycodone and morphine, minimally balanced by oxycodone metabolites with μ-activity (28). Co-administration of sub-antinociceptive doses of oxycodone and morphine produces marked antinociceptive synergy with reduced CNS side effects (24). In other experiments, repeated stimulation of κ-opioid receptors lead to the heterologous upregulation of μ-opioid receptor functions which was associated with the supersensitivity of μ-opioid receptor mediated antinociception (40). κ-opioid receptor agonists have been found to be particularly effective analgesics in experimental models of visceral pain, acting peripherally (41,42). In a multimodal, tissue-differentiated experimental pain models in humans' oxycodone showed a superior analgesic effect to morphine in visceral pain, but a similar analgesia in pain modulation of the skin and muscles (43). This differentiated effect has been attributed to the peripheral κ-agonist activity of oxycodone (44).

The effects of oxycodone and morphine are modulated differently in experimental models of bone cancer pain. The μ opioid receptor activation by oxycodone in brain regions related to pain signaling was attenuated less as compared with the effects of morphine, suggesting that modification of the μ opioid receptor is responsible for the distinct analgesic effect of oxycodone and morphine (45).

Clinical observations of opioid combinations

These findings raise the possibility of potential clinical advantages of combining several different opioids in pain management. Clinical studies were based on the rationale offered by several experimental investigations (38). The basic premise of an analgesic combination is that the two drugs operate through different mechanisms of action, so

the combination may result in a reduction in dose-related adverse effects. Although anecdotally multiple opioids are often simultaneously administered for different reasons, there are few trials assessing this specific topic. However, in an historical control study of opioid rotation and hydration, 35% of the opioid rotations were partial because of practical problems (46).

Oxycodone-morphine combination

Whereas morphine is the prototypical m-opioid agonists, behavioral antinociceptive and cross-tolerance studies indicated that pain-relieving effects of oxycodone are mediated by putative κ-opioid receptors, and an isobolographic analysis revealed marked antinociceptive synergy between these two drugs (24). These suggestive findings were supported by a clinical study of cancer patients which showed a 38% less consumption of extra-doses of morphine in patients who were administered oxycodone rather than morphine (47). In a subsequent study the improvement in the analgesic effect with the drug combination was not associated with disproportionate concomitant adverse effects such as ventilatory depression (48). However, in an experimental cold pain study morphine and oxycodone did not produce synergic antinociceptive effects in healthy humans (49), although this model was found questionable to predict clinically relevant doses of opioids (50).

Multiple combinations

The rapid need to escalate opioid doses is challenging for physicians and represents a critical phase for patients who have poor pain control despite receiving progressively increasing doses of opioids. The administration of small doses of a second opioid in patients with an unfavourable response during escalation with the prior opioid has been found effective in a preliminary report where oral morphine, transdermal fentanyl, and oral methadone were added to transdermal fentanyl, oral morphine, and oral morphine, respectively. Lower increases of equivalent doses of the second opioid, less than 20%, provided a better analgesia. Global opioid escalation index calculated in the following weeks after starting the treatment, was maintained at levels considered as acceptable, about 5 on average. Of interest, the relatively low doses of the second opioid administered did not produce adverse effects of significant intensity, while improving the analgesia (51). Thus, the second opioid added on the first one was able to brake opioid escalation in patients with pain syndrome with a poor response to the previous opioid, regardless of the combination used.

Spinal morphine and systemic buprenorphine

The combination of spinal morphine and systemic buprenorphine might be of clinical value because these opioids may interact at different levels, due to their differences in receptor activity. The antagonist effects have been reported only when high doses exceeding the therapeutic dose ranges were combined (52). The concurrent administration of spinal morphine and systemic buprenorphine produces an antinociceptive effect that was greater than what could have been predicted from individual dose-response curves. The blockade of κ-receptor by systemic buprenorphine has been hypothesized to play a role in providing superadditive analgesia with spinal morphine (53). In recent studies, buprenorphine might interact with mechanisms of hyperalgesia limiting descending facilitation mediated by spinal dynorphine expression by its κ-receptor antagonistic properties (54).

Transdermal fentanyl and other opioids

Tramadol, which is a weak opioid which acts through both monoaminergic and opioid mechanisms, has been used to facilitate dose adjustment of transdermal fentanyl in a randomized controlled study of advanced cancer patients with pain. Pain control was achieved with much slower dose escalation of fentanyl in comparison with patients receiving conventional increasing doses of fentanyl. Thus a combination of a strong opioid with a weak opioid to treat severe cancer pain allowed a more gradual increase of analgesic dosing than was possible using transdermal fentanyl alone (55).

The opioid combination of transdermal fentanyl and oral morphine has been reported in a cancer patient. The conversion from 300 μg/h of transdermal fentanyl to 150 μg/h and 360 mg of oral morphine provides effective pain control and disappearance of neuroexcitatory adverse effects. The partial opioid rotation and opioid combination were considered beneficial (56).

Conclusions

The contribution of opioid receptor regulatory mechanisms to the development of tolerance, and as a consequence a reduction of clinical analgesia, is still not clarified. To a

large degree, the uncertainty surrounding the mechanisms and consequences of regulation of opioid receptors arises from the limitations in the experimental designs in many of the studies that have investigated these events (57). The potential benefit of a combination of opioids with different receptor characteristics is even poorly explored. The complexity of opioid receptor systems, in terms of opioid heterogeneity, activities of distinct receptor types and opioid ligands, co-localization of receptor types, and the potential for ligand- and receptor-receptor interactions, and clinical situations, as well individual heterogeneity, may make difficult the application of a fascinating hypothesis which requires more experimental and clinical data.

Acknowledgements

Disclosure: The author declares no conflict of interest.

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Cite this article as: Mercadante S. Opioid combination: rationale and possible clinical applications. Ann Palliat Med 2013;2(4):189-196. doi: 10.3978/j.issn.2224-5820.2013.09.04

