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Is there enough evidence to advocate opioid combinations? Does one and one make two or more?

Abstract

Despite a more than tenfold increase in opioid consumption in the past decades, many cancer patients still suffer pain. The current understanding of this situation is poorly understood. It is still possible that in some countries pain is still undertreated, but it is also possible that we do not appreciate opioid induced toxicity and other phenomena an/or our opioid prescribing needs to be refreshed. At the moment the only evidence based tool to deal with opioid toxicity is switching to another opioid. Other methods are also described, but are far less well evidenced. However, the effects after switching are short-lived and sometimes a number of switches are needed. In this article we discuss the rationale behind and the possibility of combining different opioids with each other. Opioids are all different and opioid receptors are heterogenous. There are data to suggest that widening the activity spectrum of opioids may be the way forward in order to decrease adverse effects and maintain analgesia. At the moment there are only some data on the interaction of fentanyl and morphine, morphine and oxycodone, and buprenorphine and morphine. These data suggest that we should investigate these problems vigorously and, instead of switching from one opioid to another, we may, in future, adopt the concept of a semi-switch, where the dose of the first opioid is decreased and a second opioid is added.

Key words: opioids, combinations, interaction of opioids, pain control, morphine, fentanyl, oxycodone, buprenorphine

Adv. Pall. Med. 2010; 9, 2: 31–38

Introduction and scope

Opioids remain the mainstay of the treatment of cancer pain. They are not the ideal analgesics but we do not have anything better. Interestingly, there has been a more than tenfold increase in opioid consumption in the past decades [1] but this has not resulted in an improvement in the pain experienced by patients. In fact, the prevalence of pain in cancer patients (treated and untreated) has remained constant over the last 40 years [2]. While undoubtedly many patients with cancer pain are still under-treated, a growing number of patients may be treated too intensively and neurotoxicity is highly prevalent [3]. This neurotoxicity may include increased pain sensations, defined as opioid-induced hyperalgesia [4]. Neurotoxicity of opioids is probably due to the treatment of less opioid-sensitive pains with

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Advances in Palliative Medicine 2010, 9, 31–38
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opioids alone [5]. Failure to reduce the dose and add other, pain-mechanism-specific drugs, is still not appreciated in the primary care, where most of opioids are being prescribed.

There are a couple of mechanisms which still make us more and more aware of the shortcomings of opioids and should prompt to investigation. First of all, patients with cancer now live longer and face new challenges resulting from severe, chronic, tumour-induced and tumour-unrelated pain and need opioid therapy for a longer time than previously [6]. Opioid tolerance and other long-term effects of opioids were simply ignored by clinicians as the patients did not, usually, live long enough to develop them [7]. In this light it is interesting to note that the treatment of non-malignant pain using opioids has resulted in a new scale of observations and characterisations of long-term adverse effects [8]. Although opioids may be effective in the short term, their long-term efficacy is still debatable, probably because of their deleterious long-term effects and the development of tolerance [9]. New phenomena such as opioid neurotoxicity and cognitive impairment, including opioid-induced hyperalgesia as well as hypogonadism and osteoporosis, have been described and their presence confirmed in cancer patients [4, 10–12]. It is too early to say how important these phenomena are in analgesia overall but it seems that the scene is dramatically changing and strategies aiming at limiting the opioid dose by combination with other drugs and non-pharmacological means have become more and more interesting.

In this article the question of whether the co-administration of two opioids has the potential to increase analgesic activity with a concomitant reduction in adverse effects will be addressed. The co-prescribing of drugs other than opioids is beyond the scope of this article.

In the past, when knowledge of opioids and the opioid receptors involved in pain transmission was limited, the general advice was to use one opioid at a time and to co-administer it with non-opioids such as paracetamol or NSAIDs [13, 14]. Opioid combinations in clinical practice have never been recommended for general use and were considered by some to be a mark of poor clinical practice, as there was considerable fear that the total dose of opioids would markedly increase [15]. There was also a fear that the schemes would be too complicated and prone to errors by nurses, doctors and patients. "Keep it simple" was the advice [16, 17]. All effective analgesic opioids were seen as nearly identical and were invariably full μ-opioid-receptor agonists. The differences between opioids were unknown or simply ignored. This was also the reason why some "different" drugs such as buprenorphine are still unpopular despite their proven efficacy [18, 20].

In the light of current knowledge there are several aspects which we need to take into account. We shall discuss them here in more detail:

— the differences between opioids;
— are all clinically efficacious opioid analgesics μ-agonists? What is the role of other opioid receptors in analgesia?
— opioid receptors may be heterogeneous and different drugs may react with different variants of these receptors;
— ultra-low doses of opioid receptor antagonists may increase opioid analgesia.

After exploration of these four themes we shall review the existing evidence and make a plea for further investigations of opioid combinations as a potential improvement in opioid therapy.

Are opioids all the same or are there clinically relevant differences between them?

Opioids may differ from each other in many ways [21]. They may have various physicochemical properties and because of these behave in different ways in body fluids. For example, lipid-soluble drugs such as fentanyl and buprenorphine can be absorbed through the skin, will have a high volume of distribution and be preferentially metabolized by the liver. They will also readily cross the blood-brain barrier and act predominantly on the opioid receptors localized in the central nervous system [22–24]. In contrast, more water-soluble morphine will be readily absorbed from the gastrointestinal tract, its volume of distribution will be much smaller and it will have problems crossing the blood-brain barrier. Morphine metabolites will be excreted in the urine as glucuronides. Morphine, because of its properties, will reach high concentrations outside the central nervous system. In this way it may also contribute to peripheral opioid analgesia [25]. The physicochemical properties of the drugs will also result in different pharmacokinetic behaviour and in longer or shorter stays of the drug in the body fluids. The physicochemical properties of drugs may result in their different affinities to opioid receptors and hence speed of association and dissociation from receptors. Buprenorphine is known to have the

highest affinity to opioid receptors and the longest time of association and dissociation with and from receptors [26]. While interacting with receptors, drugs may behave as full or partial agonists or like antagonists. Full agonists, for the same pharmacodynamic effect, will occupy fewer receptors than partial agonists. In one study buprenorphine, a partial agonist, occupied five times more opioid receptors in comparison with dihydromorphine [26]. To make it even more complicated, opioids may differ in the way they influence opioid receptor metabolism after interacting with these receptors. Opioid receptors after interaction with most opioids are phosphorilated and uncoupled from the G-proteins. Only morphine-activated μ-receptors fail to undergo arrestin-dependent uncoupling from G-proteins [27]. It is thought that this unique property of morphine is related to its ability to develop tolerance. These differences are certainly clinically relevant but we still do not know how to use them to the benefit of patients. We do not know whether some opioids would be better at controlling inflammatory or neuropathic pain [13].

Are all clinically effective opioid analgesics μ-opioid-receptor agonists?

Morphine and fentanyl are seen as pure μ-opioid-receptor agonists, which means that their interactions with other than μ-opioid receptors are negligible. The same drugs are notorious for the development of tolerance. Oxycodone is probably, besides being a μ-opioid-receptor agonist, also a κ-opioid-receptor agonist [28]; while buprenorphine, besides being a μ-opioid-receptor partial agonist, is also a κ-opioid-receptor antagonist [29] and a potent agonist of the ORL1 receptor and in this way simulates the effect of pro-nociceptive dynorphin [30, 31]. This latter effect is somewhat controversial and counter-intuitive, as in a number of tests buprenorphine has been show to possess anti-hyperalgesic properties [32]. Drugs may have metabolites or isomers acting on different receptors and hence influence analgesia. Morphine's metabolite, morphine-6 β-glucuronide, is a potent opioid agonist but probably acts on a different subset of μ-opioid receptors than the parent drug [33]. Methadone's D-enantiomere has antagonistic properties at the NMDA channel receptors and hence may potentiate methadone's analgesia [34–36]. However, this mechanism is still controversial as all components of methadone analgesia can be reversed by naloxone [37].

Opioid receptors may be heterogeneous and different drugs may preferentially react with different receptor variants

Opioid receptors can be classified as mu, kappa, delta and ORL1 [38]. Although μ-opioid receptors are the most important for analgesia, all other receptors may influence analgesia directly or indirectly. Pure μ-opioid-receptor agonists are potent analgesics but show troublesome adverse effects, especially hyperalgesia and tolerance [39]. The simultaneous targeting of two or more receptor classes may offer an advantage. For example, targeting μ-opioid receptors and δ-opioid receptors produces analgesia without the development of tolerance [39]. In addition, bivalent opioid ligands targeting both μ- and delta-opioid receptors produce potent antinociception with less physical dependence and a marked reduction in the potential abuse liability relative to morphine. This could be achieved by designing new drugs which would act simultaneously on both types of receptor or the co-administration of two different drugs, each selective to one type of receptor. While the direct effect of μ-, δ- and κ-opioid-receptor activation may be analgesia, these receptors may differ in their effects on the modulation of the inflammation indirectly responsible for pain. Finley et al. have reviewed the evidence that activation of the κ-opioid receptors induces an anti-inflammatory response through the down-regulation of cytokine, chemokine and chemokine-receptor expression, while activation of μ-opioid receptors favours a pro-inflammatory response [40]. Thus, although the activation of μ-opioid receptors by specific agonists may in the short term produce analgesia, this analgesia may be followed by hyperalgesia due to activation of the inflammatory pathway.

To make the situation even more confusing, and individually unpredictable, we now know that opioid receptors come in many splice variants [41]. These splice variants may explain differences in responses to opioids. The prevalence of splice variants is still unknown but it is slowly emerging that it may differ not only from person to person, but different splice variants may coexist in one individual in different localizations in the central nervous system [42]. This may explain inter-individual and somehow unpredictable differences in responses between, for example, morphine and oxycodone [43]. Morphine may have a high efficacy when interacting with one splice variant, while its metabolite, morphine-6 β-glucuronide, may

be most efficacious when another splice variant is present [33]. Diacetylmorphine (heroin) may also interact with some MOR-1 variants in better way than morphine does [44].

Opioid receptors and their splice variants may differ between the sexes [45] as the analgesic response to opioids and their toxicity between the sexes may also be different [46].

Ultra-low doses of opioid receptor antagonists may modulate opioid analgesia

Antagonists are thought to antagonize the effects of agonists and naloxone typically abolishes analgesia evoked by full μ-opioid-receptor agonists. However, the same naloxone administered in an ultra-low dose may have a profoundly different effect. Crain et al. first described how ultra-low doses of naloxone may selectively inhibit opioid receptors that are coupled not with the Gi and Go proteins, but with the Gs proteins [47]. This latter receptor-G-protein complex, seen as involving excitatory receptors, is more sensitive to naloxone. This may result in the abolition of hyperalgesia and the improvement of analgesia, which has been shown clinically in women undergoing hysterectomy [48]. Apparently, many subsequent studies have shown either effects with a wide variation of "ultra-low" doses of naloxone or did not show this effect at all [49]. However, this research resulted in the patenting of a combination of oxycodone with the orally bio available antagonist naltrexone (Oxytrex®) and clinical studies with this drug are encouraging [50–51].

From the above discussion one thing may be obvious: a combination of opioids may, potentially, address a wider range of opioid receptors and their variants. We shall now review the existing data concerning the advantages and disadvantages of particular combinations of opioids.

Which pairs of opioids may have the potential to be more effective in the clinic?

Fentanyl and tramadol

In an open label study patients were randomized either to fentanyl alone or a fentanyl plus tramadol regime [52]. The addition of tramadol did not change anything in the level of analgesia or its adverse effects. However, it produced a marked reduction in the dose of fentanyl required to obtain an equivalent level of analgesia. The study was not geared to consider any other differences. The authors conclude that the addition of tramadol also prevented patients from requiring steep fentanyl dose increases and developing tolerance. The authors speculate that both drugs may have a synergistic effect because of the different mechanism of action of the drugs. Besides the effect on serotonin and noradrenalin transport, tramadol may have an effect similar to that of local anaesthetics inhibiting voltage-gated sodium channels [53].

Fentanyl and morphine

Fentanyl's role in the treatment of cancer pain seems well established. This drug is advocated by most comprehensive guidelines for both malignant and non-malignant pain [9, 54]. Numerous studies with this drug were conducted, although only in one controlled study was the analgesic effect of fentanyl compared with a placebo [55]. Unfortunately, in this randomized trial with 138 patients fentanyl appears not to have been more effective than the placebo. The rescue medication was slightly higher in the placebo group receiving no other analgesics (NS). Nine patients from the fentanyl and 13 patients from the placebo arm withdrew because of insufficient analgesia (NS). In the placebo group 66% and in the fentanyl group 48% (NS) revealed a lack of efficacy against pain. The results were surely not encouraging, but in the pain world what counts is the comparison with the gold standard morphine, not a placebo. Here it is enough to show that the new drug is roughly equal to morphine and has no more or, even better, fewer adverse effects. An important randomized study assessing the safety and preference of fentanyl versus controlled morphine was published in 1997 by Ahmedzai et al. [56]. In this multi-centre study patients treated with fentanyl had significantly less constipation and less drowsiness, but more sleep disturbances and shorter periods of sleep than patients treated with morphine. Patients in the fentanyl phase needed additional morphine "breakthrough" doses on 53.9% of the days, versus 41.5% of the days for the group of patients treated with controlled-release morphine ($p = 0.0005$). The doses of rescue morphine were also higher in the fentanyl phase. For patients treated with fentanyl, 47.1% needed at least one increase of the dose while this was needed in only 27.4% of patients treated with controlled morphine. It must be pointed out, however, that the trial was funded by the pharmaceutical industry. What can be the interpretation of these data now,

15 years later? Fentanyl has a higher neurotoxic potential than morphine and may be a potent analgesic but also a hyperalgesic drug [57–59]. The addition of morphine as "rescue" medication is probably needed to counteract fentanyl-induced hyperalgesia. At the time of the 1997 study nobody had yet heard of opioid-induced hyperalgesia and neurotoxicity. For many patients morphine as a second drug was not an "add-on" but a necessary step to prove or support the analgesic activity of fentanyl. Yet the pharmaceutical industry persuaded us that "the patients prefer to put a patch on than to swallow". They forgot, however, that to achieve a good result more than half of the patients needed both to put a patch on and to swallow tablets/liquids. Probably much better results would have been achieved by a combination of fentanyl patches with controlled-release morphine. However, these kinds of studies are unthinkable for a competing industry. In the light of this, it is important to cite the study by Mercadante et al. [15]. In this study patients with rapidly escalating doses of opioids (100% in the last week) were randomized either to receive a second opioid or not. There were only five patients in the fentanyl group who received additional morphine and five patients in the morphine group who received additional fentanyl. In general, in both arms of the study, the dose increment was halted and the pain scores were much improved, suggesting that the addition of the second opioid may influence the process of tolerance development. Other conclusions were impossible because of the very low number of patients included.

Morphine and oxycodone

Morphine and oxycodone clearly interact with a different sub-set of opioid receptors in the central nervous system. In particular, there is agreement that oxycodone is not only a μ-opioid-receptor agonist but also an agonist of κ-opioid receptors [60–62]. Intrathecal oxycodone has a limited analgesic potency in rats (2–7% in comparison with morphine) [63, 64] which could be translated into a clinical situation in having a much less potent effect when oxycodone is administered epidurally [65]. Oxycodone seems not to show a cross tolerance with morphine. Most of the patients who do not experience an analgesic effect from morphine, or experienced severe adverse effects, were able to obtain effective analgesia with oxycodone [43]. It is thus not surprising that the two drugs administered together may have an interesting analgesic effect, as they have different mechanisms of action [62]. The administration of both morphine and oxycodone produces much more effective analgesia with fewer CNS-related adverse effects in rats [66]. In humans this was tested in one study by Lauretti et al. [67] Twenty-six patients were treated in a double blind, randomized, cross over study of either 14 days of controlled-release morphine and 14 days controlled-release oxycodone or the other way around. Patients were allowed to use immediate-release morphine when the pain increased. Apparently, patients receiving a combination of controlled-release oxycodone and immediate-release morphine needed 38% less morphine than patients receiving a combination of two morphine preparations. Interestingly, patients receiving combination oxycodone and morphine experienced significantly less nausea and vomiting. The authors conclude that the interaction with both μ- and κ-opioid receptors was beneficial for the analgesia and side effects profile.

Buprenorphine and morphine

When buprenorphine was introduced some 30 years ago there was a high degree of anxiety about the possibility that this drug may extract and replace morphine from its receptor [26, 68]. In the eyes of many professionals, this still meant that the only valuable analgesic effect of the full agonist would be lost. Subsequently several studies were conducted which showed something quite opposite. Buprenorphine administered systemically works perfectly together with epidural morphine from which, as we know, most of the infused drug is also available systemically [69–71]. The responses are frequently supra-additive and the addition of buprenorphine to morphine does not increase the adverse effects. Mercadante et al. [72] have more recently studied the use of IV infusions of morphine for breakthrough pain controlled mainly by transdermal buprenorphine. They also conclude that the responses were encouraging and frequently supra-additive. The conclusion from these data should be that the displacement of morphine has never been described in a clinical situation. Buprenorphine and morphine (and many other opioids) can be administered together without fear of negative interaction. The benefit of the combination is, however, far from being proved. There are no data of the interaction between buprenorphine and oxycodone. It is possible that the additive effect of oxycodone (a κ-opioid-receptor agonist) could be lost because of buprenorphine's κ-opioid-receptor antagonism.

Conclusions

Combinations of opioids have been poorly researched because of the paradigm of using only one opioid at a time and because of a lack of interest in the subject from the pharmaceutical industry. This article shows that the addition of a second opioid is attractive, especially for abolishing the neuroexcitatory effects of the first. This is most probably the case with the combination of fentanyl and morphine. The whole concept of "breakthrough" medication should thus be re-investigated using this knowledge. The concept of a switch or opioid rotation from one opioid to another should be investigated according to Mercadante et al. [15], who introduced the notion of a semi-switch. In a patient with a rapid increase of tolerance and neuroexcitatory symptoms, instead of changing one opioid to another the dose of the first opioid should be decreased and a second opioid introduced. In this respect a combination of a lipophylic and a hydrophilic opioid (i.e., fentanyl-morphine, buprenorphine-morphine, methadone-morphine) are the most interesting. There are also some exciting data regarding combining morphine with oxycodone [66]. As oxycodone also acts on the κ-receptors, it is a "natural" partner for μ-opioid-receptor agonists. Inhibiting both types of receptors may offer some advantages. What should be avoided at the moment is the combination of buprenorphine and oxycodone. There are no data on this combination at all, but buprenorphine is an antagonist of the κ-opioid receptors and the greatest advantage of oxycodone κ-opioid-receptor agonism would probably be lost using this combination. The combination of agonists and ultra-low doses of antagonists is slowly coming to clinics, albeit simply because we still do not understand what exactly an "ultra-low" dose is.

The final aspect, which we did not touch on here, is that of complexity of treatment. Taking two, or maybe in the future three, different opioids may make patients more vulnerable and mistakes would be more likely. However, it is perfectly possible in future to make combinations of two controlled-release drugs in one tablet. At the moment combinations could be used as a last resort treatment in the case of rapidly developing tolerance and the loss of the analgesic potency of the drugs.

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