The Role of Controlled-Release Opioids in the Treatment of Chronic Pain

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ABSTRACT

Conventional wisdom in the field of pain management assumes that controlled-release formulations of opioid analgesics provide superior pain control, and are less prone to abuse than immediate-release formulations. Lack of evidence to support these assumptions is noted, and the issues of respective cost, convenience, efficacy, adherence, and abuse liability are analyzed. A clinical approach is proposed, prioritizing the use of immediate-release formulations.

Introduction

Controlled-release formulations of opioid analgesics are widely assumed to provide a better quality of pain relief, and to be less subject to abuse than immediate-release agents. These assumptions are not supported by evidence. The use of immediate-release formulations is recognized as a therapeutic option in treatment of chronic pain, but is currently in disfavor, mostly because of unsubstantiated concerns about abuse liability.[1,2] The respective roles that these differing formulations should play in treatment of chronic pain are analyzed on the basis of a number of considerations. These include cost, convenience, efficacy, and adherence.

Cost

While surveys reveal that the problem of undertreated pain persists as a public health disaster,[3] the dollar amount society already pays for opioid analgesics runs to more than $1 billion per year. The yearly expense of treating a single chronic pain sufferer, with controlled-release formulations, can easily surpass $100,000. It is difficult to estimate how much more opioid medication than is currently prescribed will ultimately be required in order to resolve the problem of undertreated pain. The amount that will be needed could turn out to be orders of magnitude higher than what is currently used. If the problem is addressed primarily through the use of controlled-release formulations, the costs will be staggering.

Convenience

Convenient dosing intervals make the prescription of controlled-release formulations an option worthy of consideration when treating selected patients, for whom it is felt the benefits outweigh the increased cost. The advantage of enjoying longer sleep intervals, uninterrupted by pain, is an example of such a situation.[4] If funds are short, the same benefit might be realized by setting an alarm clock, and taking a dose of an immediate-release opioid in the middle of the night.

Efficacy

Evidence from numerous studies indicates that reductions in pain levels are the same milligram-for-milligram, regardless of whether immediate-release or controlled-release formulations are employed.[5,6]

Analysis of studies utilizing patient-controlled analgesia (PCA) suggests possibilities concerning the issue of comparative efficacy of one formulation over the other.

Conventional PCA serves as a model for the use of immediate-release agents in the treatment of chronic pain. Studies evaluating the treatment of acute post-surgical pain, accomplished through conventional PCA, reveal that pain can be safely and effectively managed with intermittent self-administration of small boluses of opioid analgesics.[7-9] Total dosages remain lower, when this technique is employed, than when fixed schedule dosing or continuous infusions are employed.

The conventional approach to PCA, employing intermittent boluses, was compared to the constant infusion of morphine, in a protocol that allowed patients to control the infusion rate of their medication. In effect, patients were allowed to titrate their blood levels upwards when pain occurred. This approach is called pharmacokinetically based patient-controlled analgesia, PKPCA. The PKPCA group in the study used more total medication, experienced the same incidence of adverse side effects, and had better outcomes than the conventional PCA group.[10] This version of PKPCA would serve as the model for a scenario in which controlled-release agents were titrated to the endpoint of eliminating breakthrough pain, by patients empowered to exercise the principle of patient-controlled analgesia.

An intriguing possibility is raised by the successes encountered during the use of this PKPCA approach. This is the hypothesis that the maintenance of opioid blood levels higher than those typically achieved during the course of more usual treatments is responsible for the improved outcomes. In the future, controlled-release formulations might turn out to be particularly effective, if employed in this manner. This possibility will be discussed later in some detail.

The PKPCA study results debunk a fear universally held by doctors–that patients, if given the opportunity, will lose control and take too much medication. Instead, it appears that when presented with the opportunity to use enough medication to obtain the best possible therapeutic outcome, many patients fail to do so.

For the sake of completeness, is should be noted that there are a couple of studies suggesting improved outcomes in patients treated with controlled-release opioids for post-operative pain. These studies are probably of little relevance to the treatment of chronic pain.[11,12]

Adherence

In the practice of clinical medicine, the use of any sort of controlled-release formulation improves, as a general rule, patient adherence to treatment regimens. This occurs because patients are more likely to remember to take their medications when they only have to do so once or twice a day. The treatment of pain is probably an exception to this generalization. The notion that a pain sufferer would fail to adhere to his treatment regimen, by forgetting to take his medication, is less than credible, because pain has a way of reminding its victims to take their pills. A special case, in which a problem with

adherence might reasonably favor the selection of a controlled-release formulation, is the treatment of Alzheimer's disease. It is conceivable that research will eventually demonstrate some benefit that may be derived from improved adherence, when controlled-release opioids are administered under advantageous conditions.

Abuse Liability

Controlled-release formulations of opioids are widely assumed to carry a reduced risk of abuse. There is no evidence to indicate that this is actually the case. There is also no evidence demonstrating that there is *any* significant risk of opioid addiction when these substances are employed in the treatment of chronic pain.

> In terms of the question of what is the incidence of new cases of addiction in patients who were not previously addicted resulting from the therapeutic exposure to opioids for the treatment of chronic pain, the answer is that there are no studies that address that issue. It is not that there are conflicting studies. It is that there are no studies.[13]

A good quality of evidence concerning the potential for opioid abuse, when these substances are employed in the treatment of chronic pain, is derived from the basic sciences. Key elements of neuroanatomy and physiology are reviewed, as a grasp of this information works to dispel the commonly held misconception that opioid abuse is likely to result from pain treatment employing opioids.

Pain is modulated mainly by two opioid-mediated systems within the central nervous system. These systems are anatomically and physiologically distinct. The brain-based system is responsive to low doses of opioids, and drops out of the picture at higher dosages, because of tolerance. The spinal cord-based system responds to higher dosages without developing treatment-limiting tolerance:

The brain-based pain modulating system is activated by opioid receptors found in the periaqueductal gray matter of the mid-brain, and in the raphe nucleus of the brainstem. This system modulates the transmission of pain signals by sending inhibitory messages down the descending pathways of the spinal cord.[14] Within this system, tolerance to the pain-modulating effects of opioids is thought to develop in a linear fashion.[15]

Chronic pain is often successfully treated with dosages of opioids orders of magnitude larger than those required to activate the brain-based system. The opioid receptors mediating this effect are found in the dorsal horn of the spinal cord. Development of tolerance within this system, if it occurs at all, does not interfere with the clinical success of long-term treatment with opioids.[16]

A dosage ceiling exists, beyond which rising blood levels of opioids do not produce euphoria or other psychological effects. The existence of this ceiling is inferred from empirical observations of patients enrolled in methadone maintenance programs. The dosage at which this phenomenon occurs is roughly within the range of 100 milligrams per day of methadone.[17] Patients suffering from chronic pain often require dosages of opioids well above any such ceiling. This prevents the occurrence of the psychological rewards, which are associated with lower, less frequent dosages of opioids.

In summary, when opioids are employed in the treatment of chronic pain, the intrinsic design of the central nervous system mitigates against abuse, regardless of the formulation of the medication used.

Public Health

In the context of the diversion of pharmaceuticals, there is effectively no such thing as a controlled-release version of an opioid analgesic. Determined abusers invariably find ways to defeat the time-release provisions built into these formulations. In fact, strategies such as crushing the pills can be picked up by anyone who watches the evening news on television. The large amount of opioid contained in controlled-release products exposes unwary, opioid-naïve abusers to the risks of respiratory depression and death, particularly when these substances are consumed in combination with alcohol, or tranquilizers.[18]

Apart from the danger that high-dose formulations pose to uninformed opioid-naïve abusers, the safety of children living in households where these formulations are present must be considered. In the absence of evidence establishing that high-dose formulations of controlled-release opioids produce superior therapeutic outcomes, the existence of these products cannot be justified. Consequently, opioid analgesics should not routinely be manufactured in either controlled-release, or in immediate-release formulations larger than the equivalent of 20-30 mg of morphine. Patients who require higher dosages can easily ingest more pills.

Integration of Basic Principles

The routine integration of basic principles into the management of chronic pain would bring the treatment of this disease closer to the medical mainstream, which approaches diseases ranging from depression to hypertension with the goal of effecting a cure, or at the very least a remission. Similar goals, if established for the treatment of chronic pain, would employ the principles of preemptive analgesia, titration, and patient-controlled analgesia.

The principle of *preemptive analgesia* is a concept whose value has been established by studies evaluating responses to, and outcomes resulting from the treatment of acute post-surgical pain.[19] There is no consensus regarding the application of this principle to the management of chronic pain. This is reflected by existing confusion about whether one should address the occurrence of breakthrough pain with rescue doses of immediate-release opioids, or control it with further titration of controlled-release agents. If results from the PKPCA study were applied to this issue, one would infer that superior outcomes might result from the aggressive titration of controlled-release opioids, to the endpoint of eliminating breakthrough pain.

In treatment of outpatients, the principle of *patient-controlled analgesia* finds limited expression in the use of rescue doses of immediate-release agents, employed to treat episodes breakthrough pain. The beneficial outcomes observed in the PKPCA study suggest that a broader application of this principle might be of benefit in the treatment of chronic pain. In order to realize such a benefit, the principle of PCA would have to be applied in combination with the principle of *titration to therapeutic effect*. This is a radical suggestion, because it implies that in order to achieve optimal therapeutic outcomes *pain victims may have to be empowered to use as much opioid medication as they think they need*.

A Direction for Research

While there is no research indicating that controlled-release opioid formulations produce superior treatment outcomes in any chronic pain population, available evidence suggests that this class of pharmaceuticals, if used under the right circumstances, might hold that potential. Such a study would test the hypothesis that superior treatment outcomes result from the achievement and

maintenance of blood opioid levels higher than those usually attained. Such a study would have to meet the following conditions:

1. In an expression of the principle of preemptive analgesia, the goal of treatment should be to titrate beyond the usual therapeutic endpoint of optimal functioning to the endpoint of eliminating breakthrough pain.

2. The principle of patient-controlled analgesia should be used in accomplishing titration to this endpoint. This would necessitate a shift away from the current paradigm of limiting opioid dosages whenever possible, a convention that effectively assures the ongoing undertreatment of chronic pain.

3. Measurements of efficacy should include: (a) reduction in pain levels; (b) improvements in function; (c) eventual reduction of dosage; and (d) resolution of disease.

4. A control group should be instructed to titrate to the same endpoint, using immediate-release opioids.

Dosage reduction is included as a measure of efficacy because in the author's experience, a number of patients who were aggressively titrated to full activity levels, resulting from oxycodone intakes in the range of thousands of milligrams per day, spontaneously decreased their opioid consumption after several months of this treatment, without experiencing any corresponding loss of improvements in the functioning that they had gained. This observation raises the intriguing possibility that cures of some chronic pain states may be possible through a correct application of the principle of titration to therapeutic effect, as long as the principle of patient-controlled analgesia is applied as well. This possibility is bolstered by anecdotal reports of cures of chronic regional pain syndrome, resulting from infusion of intrathecal opioids by implanted pumps.

Patients suffering from severely neglected long-term chronic pain would seem to be the best focus for this sort of research, as this group has the most to gain from an aggressive approach to titration.

Conclusions

The roles that the two formulations of opioid analgesics will ultimately play in the treatment of chronic pain remains to be determined. For now, the evidence suggests several conclusions:

1. Dogmatic insistence on first-line use of controlled-release opioid analgesics should cease. In the absence of convincing evidence that these formulations produce superior outcomes, the expenses and risks associated with their first-line status cannot be justified.

2. The option of using immediate-release agents should be removed from its disfavored status. This option should be regarded as preferred first-line treatment.

3. Controlled-release opioids should remain a therapeutic option, available to be employed in the treatment of selected patients, in situations where therapeutic benefits are thought to outweigh the increased expense of these formulations.

4. Neither controlled-release formulations nor immediate-release formulations of opioids should be produced in dosages larger than the equivalent of 20-30 mg of morphine. The existence of these higher dose formulations poses unjustifiable risks to opioid-naïve abusers, and to children at risk for accidental ingestions.

5. Improved therapeutic outcomes may result from the titration to and maintenance of blood levels of opioids higher than those typically achieved during usual forms of opioid therapy. This hypothesis should be investigated through studies that vigorously exercise the principles of preemptive analgesia, titration, and patient-controlled analgesia.

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