Critical Reviews in Oncology/Hematology 99 (2016) 241–248

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Opioid switching in cancer pain: From the beginning to nowadays☆

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ARTICLE INFO

Article history:
Received 4 August 2015
Received in revised form 2 November 2015
Accepted 22 December 2015

Keywords:
Cancer pain
Opioid switching
Opioid rotation

ABSTRACT

Opioid switching is the process of changing from one opioid to another to obtain a satisfactory clinical balance between analgesia and adverse effects. This pharmacological technique has been introduced about 20 years ago to enhance the opioid response in advanced cancer patients with chronic pain. More information is now available. This review will examine many different aspects of opioid switching, including the history and evolution through the last decades, some clinical aspects based on the most recent experience, controversies on the indications, conversion ratios and modalities of switching in some specific circumstances, and evidence based recommendations.

Contents

☆ The work has never been presented in any meeting.

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http://dx.doi.org/10.1016/j.critrevonc.2015.12.011
1040-8428/

1. Introduction

Opioid therapy is often necessary to control pain in the majority of cancer patients during the course of their illness. Opioids are the cornerstone of cancer pain management and their use has been increasing in the last years. Cancer pain is commonly treated effectively with opioids administered at regular intervals and providing rescue doses for the management of breakthrough pain [1]. There is no single opioid of choice for all patients, but one opioid can be optimal for an individual patient [2,3]. As physicians cannot predict a patients' treatment response, previous opioid exposure can be considered as a therapeutic trial that allows the determination of the individual response. After starting the prescribed initial opioid, clinical efficacy may decrease gradually in time or even abruptly, resulting in a need for dose increase. In some cases dose increases do not provide analgesia, and further dose increments are ineffective. Alternatively, adverse effects may occur that are difficult to control with symptomatic therapies [4].

If an opioid fails to provide adequate analgesia or causes unmanageable adverse effects, this agent has to be stopped and a different opioid should be offered [5]. Opioid switching (also known as opioid rotation) is the process of substituting one opioid for another one to improve the opioid response, either improving pain relief or reducing the intensity of adverse effects [6]. New opioid analgesics have been introduced in the last years and may have a potential role in improving the opioid response [7].

This review will examine many different aspects of opioid switching in cancer patients with pain, including the history and evolution through the last 20 years, some clinical aspects based on the acquired experience, controversies on the use, and evidence based recommendations of opioid switching.

2. Background regarding differences among opioids

2.1. Pharmacodynamic aspects

Opioid receptor genetics. In animal models and humans, genetic differences in the opioid receptors and their affinities for various opioids have been shown. Opioid receptors may have polymorphisms, including variants that alter amino acid sequence of the receptor as well as properties of receptor functions. Some variants may exhibit altered binding affinities to different opioids. Receptors subtypes are likely to be receptor dimers with different signaling and trafficking relative to monomers [8]. While poor opioid tolerability due to genetic make-up is expected to manifest early, the expression of genetic differences may be consequent to progressive changes in receptor subtype densities and receptor-effector relationship after opioid exposure and/or progression of disease. Thus, the opioid response may change in time due to different mechanisms. There is evidence to suggest that opioid receptor mutations may contribute to inter-individual variability of the clinical effects of opioids [9].

The mu-receptor opioid agonists have been traditionally considered similar to morphine in respect to their mechanism of action. In last decades, several experimental studies have challenged this assertion. The repeated administration of opioids leads to the development of tolerance. that may shift the dose-response curve to the right. Pharmacodynamic tolerance is often assumed to refer to a process of neural adaptation. Tolerance development to analgesic and toxic effects has been shown to be dissociated in time, and the magnitude of cross-tolerance between opioids can vary for the analgesic and toxic effects [4]. When tolerance to adverse effects does not develop to the same extent as for analgesia, the escalating opioid dose required for maintaining analgesia may reach a level where adverse effects become dominant and troublesome. Variable analgesic or adverse effect response to different opioid analgesics is relatively common and is probably due to incomplete cross-tolerance among opioids. This phenomenon is frequently attributed to differential opioid receptor affinities. Tolerance develops independently at each receptor subtype in response to the binding of a drug and its intrinsic activity. The development of analgesic tolerance may be due several conditions. Chronic receptor activation induces a reduced sensitivity for the agonist and adaptation of the neuronal system by the expression of compensating mechanisms [10]. Changes in the receptor-effect relationship may also occur over the course of the illness with prolonged opioid exposure, resulting in a change in the ratio of analgesic-toxic effects. An individual receptor profile and specific clinical conditions may influence the final effects in terms of analgesia or side effects .The phenomenon of asymmetric cross-tolerance could also be due to differences in agonist efficacies, rather than receptor selectivities. To generate a given effect it is necessary to occupy a number of receptors out of the total population, the so called "fractional receptor occupancy". The number of receptors to be occupied is inversely proportional to the intrinsic activity. The amount of the remaining un-occupied receptors (receptor reserve) depends on this property. The larger the receptor reserve, the greater the intrinsic efficacy [11]. For example, it has been shown that morphine has a high occupancy requirement and is considered a relatively low intrinsic-efficacy agonist. These observations may explain the loss of efficacy with increasing doses of morphine. Fentanyl, as a high efficacy opioid, has lower fractional receptor occupancy and lower tendency to decrease opioid receptor expression in periaqueductal gray of rats as compared to morphine. With equianalgesic doses, switching to fentanyl produced antinociceptive effectiveness in rats tolerant to morphine [12]. A switching to an alternative opioid with a higher efficacy may reverse the reduced response to morphine. Different opioids bind to different regions of mu-receptor and may bind with weaker activity to other opioid receptors. Morphine metabolites, namely M6G, may produce peculiar toxicity according to genetic variation of opioid receptor [2].

Different opioids produce different effects through unique conformational changes of the opioid receptor [13]. They include, for example, differences in G-protein interactions, receptor phosphorylation, and β-arrestin activity [14]. As a consequence, allosteric modulation, ligands signaling bias, and mu opioid receptor subtypes or dimmers may contribute for giving a rationale to opioid switching in an attempt to improve the clinical response [15].

According to these observations, the long-term use of opioids is likely to produce continued development of tolerance over time requiring progressive dose increase to maintain pain relief. In contrast, it is often reported that patients can be maintained for long periods of time at constant drug doses. These contrasting data have been reconciled by recent studies, in which morphine tolerance progressed for some weeks and then stabilized. Compensatory mechanisms to minimize tolerance may include changes in the levels of mu-opioid receptors in specific regions of the brain. It is likely that receptor variants, possibly genetically determined may influence the balance between forces producing tolerance and expression of new receptors [16].

A diminishing opioid analgesic efficacy during opioid treatment is often considered a sign of pharmacological tolerance, assuming that there is not apparent increase in pain input or progression of disease. Escalation of opioid doses is a common approach to reproduce the same level of analgesia. However, this practice may result in unexpected biochemical changes, as in some cases pain may increase rather than decreasing. Clinical reports suggest that opioids, intended to abolish pain, can unexpectedly produce abnormal heightened pain sensations, which are characterized by a