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GENERAL AND SUPPORTIVE CARE

Opioid switching: A systematic and critical review

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Summary Cancer patients with pain may not respond to increasing doses of opioids because they develop adverse effects before achieving an acceptable analgesia, or the analgesic response is poor, despite a rapid dose escalation. Opioid switching may significantly improve the balance between analgesia and adverse effects. We conducted a systematic review of existing literature on opioid switching.

According to available data, opioid switching results in clinical improvement in more than 50% of patients with chronic pain with poor response to one opioid. However, data are based on open studies or small case series. Reasons for switching may influence the dose of the alternative drug. Opioid conversion should not be a mere mathematical calculation, but just a part of a more comprehensive evaluation of pain, adverse effect intensity, comorbidities, and concomitant drugs. The process of reaching an optimal dose should be highly individualized, particularly when patients are switched from high doses of opioids, given the wide conversion ratios reported in literature.

Introduction

According to World health Organization guidelines, opioid analgesics are the mainstay of cancer pain management.[1] Oral morphine has been widely used for treating pain of moderate to severe intensity, and remains the opioid of choice for its familiarity, availability, costs rather than proven superiority.[2]

However, some patients may not respond to increasing doses of morphine, due to adverse effects before achieving an acceptable analgesia, or poor analgesic response despite rapid dose escalation. Although opioids have no known ceiling associated with their dosing a more liberal use has resulted in clinical reports of very high morphine doses causing

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new forms of opioid neuro excitatory toxicity in these cases. Clinicians should be prepared to be skilled in using alternative opioids. The frequency of opioid switching tends to increase in acute palliative care units, probably as a consequence of a better knowledge and an improved monitoring of the cognitive function in patients who receive higher doses of opioids than in the past.[3]

A substantial minority of patients treated with oral morphine (10—30%) do not have a successful outcome because of excessive adverse effects, inadequate analgesia, or a combination of both adverse effects along with inadequate analgesia.[4] It is now recognized that individual patients vary greatly in their response to different opioids. Patients who obtain poor response to one opioid will frequently tolerate another opioid. Sequential opioid trials, also opioid rotation, or opioid switching may be needed to identify the drug that yields the most favorable balance between analgesia and adverse effects.[5] The biological basis for the individual variability in sensitivity to opioids is multifactorial and has been described elsewhere, although some aspects remain unclear.[6]

The need to change opioid occurs in the following clinical conditions: (a) pain is controlled but the patient experiences intolerable adverse effects; (b) pain is not adequately controlled, but it is impossible to increase the dose due to adverse effects; (c) pain is not adequately controlled by rapid increasing the dose of opioids, although the drug does not produce adverse effects. This last point remains controversial, as further increasing doses could potentially allow achieving the appropriate analgesia. However, a rapid opioid escalation has been recognized as a negative factor for the clinical response.[7]

These issues have been the subject of several reports. Other than examining the obvious evidence that opioid switching is largely anecdotal or based on observational and uncontrolled studies,[8] the aim of this study was to critically review data existing on the clinical benefit of such pharmacological techniques, and to draw possible practical indications on how to convert the doses in the different clinical conditions.

Methods

A systematic search of the English literature was conducted consulting the following databases: MEDLINE, PUBMED, CANCERLIT, and EMBASE. A free-text search method was used including the following words and their combination: opioids, switching, substitution, rotation, and cancer pain. The inclusion criteria consisted of retrospective and prospective trials that employed multiple opioid use for treating cancer pain, also including series of at least 10 patients. Studies where it was not possible to recognize the sequence of drugs were not considered in calculation, and were commented on the basis of the available data. Comparative studies in different arms, letters or case reports including few patients were excluded.

Results

A total of thirty-one reports with the inclusion criteria were identified in the research. Given the complex nature of the topic, it was expected a generally low quality of included trials, based on existing quality items checklists.[9,10] For this reason no attempt for meta-analysis was done. The more frequent indication for opioid switching was uncontrolled pain with/or adverse effects, although the distinction was not always clear among studies. Two studies reported on 129 patients who were switched from morphine to hydromorphone and vice versa. Two studies reported an experience of switching to subcutaneous oxycodone in 32 patients. Four studies included 458 patients who were switched from oral morphine to transdermal fentanyl. Small series have reported on the switching from morphine and other opioids to subcutaneous fentanyl. Switching to methadone has received the largest attention in literature. Thirteen studies, of which three were retrospective, analyzed 513 patients who were switched from different opioids to methadone. Of these, 60 patients were receiving fentanyl before switching to methadone (19 and 41 patients, from intravenous to intravenous route, and from transdermal to oral route, respectively). Data of these studies were classified when it was possible to extrapolate pooling data (see Table 1). Small series, even though reviewed for comments, were not included in Table 1. Only one study dealt with opioid substitution in children.

General issues

The first large series published on opioid rotation included 80 patients undergoing to 111 episodes of opioid rotation.[11] The main indication for changing opioid was the presence of adverse effects, such as cognitive failure, hallucinations, myoclonus, and nausea (92 patients). A minority of patients had uncontrolled pain or rectal irritation with methadone suppositories. Most patients were receiving morphine and were mostly switched to hydromorphone. The leading symptoms improved in 73% of