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The long and winding road of non steroidal antinflammatory drugs and paracetamol in cancer pain management: A critical review

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Abstract

The aim of this review was to assess the value of NSAIDs and paracetamol in patients with cancer pain to update a previous review performed ten years ago on this topic. The approach was analytic and based on clinical considerations, rather than on raw evidence, which often does not provide useful information in clinical practice. Both published reports from an extensive search of electronic data bases were collected from January 2001 to December 2011. A free-text search method was used including the following words and their combination: "Anti-inflammatory drugs OR paracetamol OR acetaminophen" AND/OR "cancer pain". Any randomized-controlled trial was considered.

Thirteen reports fulfitted inclusion criteria in this systematic review. Randomized trials have been performed by using different modalities of intervention. Single drugs added on opioid therapy or during opioid substitution with opioids as rescue drugs through a patient controlled analgesia, were compared with placebo or between them. Five studies regarded paracetamol. Other four studies assessed the efficacy dipyrone, ketorolac, dexketoprofen, and subcutaneous ketoprofen in cancer pain management, mainly on top of an opioid regimen. The role of paracetamol and NSAIDs in the management of cancer pain still remains controversial. The papers published in this last decade were unable to answer the main questions. There is no proof that they should be used to start the treatment and how long they should be administered when opioid treatment is added on top. While paracetamol seems to be devoid of any benefit, particularly if given at usual clinical doses which should be less than 4 g/day, ketorolac seems to provide an additive analgesic effect even in patients receiving different doses of opioids. The main indication from the analysis of these data is that NSAIDs could be given in patients receiving opioids, evaluating their benefit and weight on opioid therapy in individual patients who have a favorable response to justify a prolonged use.

Keywords: Cancer pain; Anti-inflammatory drugs; Paracetamol

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1. Introduction

According to the World Health Organization (WHO), non steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (PAR) are prescribed alone as first step, or in association to opioids for the subsequent analgesic ladder steps [1]. The rationale for adding this class of drugs to an opioid regimen is to improve the balance between analgesia and adverse effects by either increasing analgesia without adding adverse effects or by maintaining analgesia with less adverse effects, providing an opioid-sparing effect. Concerns about NSAIDs are related to their adverse effects and the use of this class of drugs remains debatable, particularly when they are used first, and then continued with opioids in the other steps in the long-term treatment, when their efficacy cannot be evaluated due to the analgesic covering offered by opioids, or in elderly [2]. Evidence-based reviews often provide raw data which do not seem always applicable in the clinical setting due to the rigid criteria of selection. For example, conclusions suggesting to increase the dose of NSAIDs to a maximum acceptable dose [3] may be not advisable from a clinical point of view. Moreover, these reviews focused on the level of methodology [4], rather than the clinical rationale of the study, which is fundamental for a consequent clinical application in daily practice. Finally, many studies reviewed were really old in terms of methodology, questions posed, and drugs used. The aim of this review was to assess the value of NSAIDs and paracetamol in patients with cancer pain to update a previous review performed ten years ago on this topic [5]. The approach was analytic and based on clinical considerations, rather than on raw evidence, which often does not provide useful information in clinical practice (Tables 1 and 2).

2. Methods

Both published reports from an extensive search of electronic data bases, including MEDLINE, PUBMED, CANCERLIT, and EMBASE were collected from January 2001 to December 2011. A free-text search method was used including the following words and their combination: "Anti-inflammatory drugs OR paracetamol OR acetaminophen" AND/OR "cancer pain". Hand searching of relevant journals, and European conference proceedings were also considered. The references of all relevant reports and review articles were searched for additional trials. The inclusion criteria was randomized-controlled trial performed in cancer patients.

3. Results

The literature search retrieved 3703 papers. All abstracts were read by the authors and thirteen reports fulfitted inclusion criteria in this systematic review. Four papers were not considered, as paracetamol was used in combination with hydrocodone and compared with tramadol [6], in combination with codeine and compared with hydrocodone-paracetamol [7], and in combination with oxycodone and compared with placebo in patients who were receiving discrete doses of transdermal fentanyl or morphine [8], and in another study ibuprofen was included in a compound containing cobrotoxin and tramadol [9]. Randomized trials have been performed by using different modalities of intervention. Single drugs added on opioid therapy or during opioid substitution with opioids as rescue drugs through a patient controlled analgesia, were compared with placebo or between them. Five studies regarded paracetamol. Other four studies assessed the efficacy dipyrone, ketorolac, dexketoprofen, subcutaneous ketoprofen, in cancer pain management, mainly on top of an opioid regimen.

4. Discussion

In a previous review updated to 2001, the evidence from clinical trials available at that time was of limited amount and

Table 1
Studies of paracetamol. R (randomized), DB (double blind), CO (crossover), P (parallel).

Authors	No.	Design	Drug - doses	Results	Comments
Axelsson (2003)	30	DB CO 7 days	Paracetamol 4 g versus Placebo	No differences in pain intensity	Pain level too low High doses of paracetamol
Stockler (2004)	30	DB CO 2 days	Paracetamol 5 g versus Placebo	Significant differences in pain intensity	High doses of paracetamol Differences clinically not significant
Tasmacouglu (2009)	43	DB P 24 h	Paracetamol 4 g Morphine PCA versus Placebo Morphine PCA	No differences in opioid consumption or pain intensity	High doses of paracetamol
Israel (2010)	22	DB CO 4 days	Paracetamol 2g versus Placebo	No differences in pain intensity	Pain was already controlled with mean doses of 255 mg of oral morphine
Cubero (2010)	50	DB P 7 days	Paracetamol 1.5 g versus Placebo	No benefit in analgesia or time to stabilization	Add-on opioid switching to methadone. No data on final doses of methadone