World Health Organization guidelines for cancer pain: a reappraisal

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Pain is a prevalent symptom experienced by at least 30% of patients undergoing an oncological treatment for metastatic disease and by more than 70% of advanced cancer patients [1]. In 1986 the World Health Organization [2] published a set of guidelines for cancer pain management based on the three-step analgesic ladder [2]. The main aim of WHO guidelines was to legitimize the prescribing of strong opioids, arising from evidence of poor management of cancer pain, due to reluctance of health care professionals, institutions, and government to use opioids because of fears of addition, tolerance and illegal abuse.

Its application is reported to achieve satisfactory pain relief in up to 90% of patients with cancer pain. Despite the large experience proving the feasibility and efficacy [3–5], in the years of evidence-based medicine, the three-step ladder has been criticized for the lack of robust data supporting this approach. Studies validating the WHO analgesic ladder had methodologic limitations including the circumstances during which assessment were made, small sample size, retrospective analyses, high rate of exclusions and dropout, inadequate follow-up, and a lack comparison with levels of analgesia before the introduction of the analgesic ladder [6].

Thus, different problems are unresolved due a lack of controlled studies on this subject. These problems include, for example, a better definition of the role of NSAIDs, the prolonged use of NSAIDs in cancer pain, and the utility of step 2. Moreover, the indications for using different strong opioids and alternate routes of administration to improve pain relief in difficult pain situations are not well established. The proportion of patients who do not benefit from these treatments remain unclear, and how the opioid response may be improved with the use of adjuvants is also uncertain. Finally, different countries apply the WHO ladder approach differently depending on the availability of drugs.

First step

The first step in the WHO analgesic ladder involves the use of a nonopioid with or without an adjuvant analgesic. Studies of various non-opioid analgesics, combined or not with opioids were recently assessed. Heterogeneity of study designs and outcomes, and short length of study precluded meta-analyses.

From data available non-opioid analgesics appeared more effective than placebo. No superior safety or efficacy was demonstrated for one of this class of drugs, and slight advantages where found in trials of combinations of an non-opioid analgesic with an opioid, compared with either single entity [7, 8]. Some studies suggest a different place of non-opioid analgesics, administered in patients already on opioids, given first, to reinforce analgesia in patients with difficult pain control or who tend to develop adverse effects with increasing doses of opioids [9]. The conclusions of this study are intriguing, because the reluctance of North American physicians to use NSAIDs and conversely the extensive, and sometime exaggerated, use in European countries may find a compromise based on the data pointed out in this work. Patients could be started on opioids alone and then added non-opioid analgesics, for example in conditions where pain is particularly sensitive to this class of drugs, or to reduce the tendency to further opioid escalation, when adverse effects tend to develop.

NSAIDs are considered be effective in some specific cancer pain syndromes, such as bony metastases, although data to support this do not exist. Recent studies have shown that NSAIDs are equally effective in both visceral and somatic pain syndromes [10].

Although adverse effects occurred infrequently in previous large experiences, these studies did not specifically assess this issue. The development of ulcer or renal toxicity might not be apparent with short-term dosing [7], and the specific long-term safety profile has never been established in a randomized studies.

Second step

The role of so-called ‘weak opioids’ in the treatment of moderate cancer pain has been questioned, and it has been speculated that this step could be by-passed. A meta-analysis [11]
reported that no significant differences in pain relief were noted when the use of non-opioids alone was compared to non-opioids plus opioids for moderate pain. However, these results were based on single-dose studies or studies involving a small number of patients, and a regular clinical use would be more effective than would be predicted on data involving single-dose administration. Previous studies underlined the role of opioids for moderate pain (namely codeine, dextropropoxyphene, and codeine), in comparison to morphine in terms of efficacy and adverse effects. In opioid-naive-patients, a more favorable balance between side effects and analgesia occurred when step 2 opioids were administered compared to low doses of morphine used to omit Step 2 of the analgesia ladder [12, 13].

On the other hand, other studies assessed the use of strong opioids in opioid naive patients, that is skipping the second step drugs. Doses of 25 μg/h of fentanyl have been used successfully [14, 15], although it means to administer equivalent doses of 60 mg/day of oral morphine, which is a considerable dosage for opioid-naive patients, having a high risk to produce adverse effects and reduce patient’s compliance. This observation was confirmed in a study where transdermal fentanyl used at doses of 25 μg/h, equivalent to 60 mg of oral morphine, was better tolerated in codeine using patients rather than in opioid-naive patients [16].

In a more recent study the sequential treatment proposed by WHO was compared with a direct administration of strong opioid as a first step. Treatments appeared equally effective, although the group treated with opioids first had a better pain relief and patients’ satisfaction, and less number of therapeutic interventions. However, nausea was more frequently reported. Only 50% of patients in control group needed strong opioids in doses similar to those used in patients who received strong opioids first [17]. Unfortunately initial doses of strong opioids were not mentioned, making evaluation of data difficult. The choice of the initial doses makes the difference in terms of compliance, efficacy, and tolerability. Doses of morphine, or other strong opioids should as flexible and low as those in the range commonly used of opioids for moderate pain.

Personal experience on the use of low dose morphine

Morphine used at very low doses in opioid-naive patients may offer different advantages, including a greater tolerability while providing analgesia. The rationale was to replace opioids for moderate pain with morphine used in doses equivalent to the range of doses commonly prescribed at flexible doses in clinical practice. This approach has been prospectively evaluated in a sample of consecutive advanced cancer patients, including very old patients and preliminary data are presented. Forty-five opioid-naive patients with a pain intensity in the range of 4–7 on a numerical scale from 0 to 10, received initial doses of 12 mg divided in 5–6 doses per day (patients aged m > 70 years received 10 mg/day). Patients receiving this approach were titrated and achieved stabilization in a few days, and doses were maintained relatively constant one month after starting the therapy, with an mean final doses of 40 mg, and a calculated escalation index (OEI) <5. OEI is the mean increase of opioid dosage percentage using the following formula:

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\text{OEI} = \frac{\text{last opioid dose} - \text{starting dose}}{\text{starting dose}} \times 100.
\]

The value reported is considered devoid of risk in previous experiences with chronic opioid dosing, that is a limited need to escalate the dose [18]. Of interest tolerability was excellent with a low number of patients who discontinued morphine and required alternative drugs (4 patients, <10%). This approach has been proved feasible, effective and well tolerated, and not associated with abnormal requirements of increasing doses, although this finding should be confirmed in controlled studies. Of course, patients with severe pain are already candidates to receive strong opioids at a consistent dose of about 60 mg/day of oral morphine equivalents, according to the WHO guidelines, so that this approach should be reserved to patients with moderate pain, potentially requiring step drugs.

Third step

Morphine is the most frequently used opioid in cancer pain management. Although morphine remains a cornerstone for the management of cancer pain, due to the largest experience existing among physicians and widely availability in a variety of formulation, no clear data exist about the superiority of one opioid over another [19]. Individualization of therapy has been emphasized to minimize the side effects and to improve the opioid response. 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 [20]. It is now recognized that individual patients vary greatly in their response to different opioids. Patients who obtain poor analgesic efficacy or tolerability with one opioid will frequently tolerate another opioid. A shift from one opioid to another is recommended when the adverse effect/analgesic equation is skewed towards the side effect component, despite an aggressive adjuvant treatment. Opioid rotation has been shown to be useful in opening the therapeutic window and in establishing a more advantageous analgesia/toxicity relationship. By substituting opioids and using lower doses than expected (according to equivalency conversion tables), it is possible in most cases to not only reduce or relieve the symptoms of opioid toxicity and to manage patients who are highly tolerant to previously used opioids, but also to improve analgesia and thus the opioid responsiveness. This strategy uses much lower doses of alternative opioids in patients who are unresponsive to high doses of morphine. Drugs commonly used for opioid rotation include hydromorphone, oxycodone, and methadone [21]. The biological basis for the individual variability in sensitivity to opioids is multifactorial and has been described elsewhere, although some aspects remain unclear [22]. Although the conversion ratio between opioids in such circumstances remains unpredictable, morphine, oxycodone, and hydromorphone
seem to be more manageable in the clinical context. Of interest, differently from other opioids, methadone, which is chemically distinct from morphine, oxycodone, or hydromorphone, shows some particularities which make this drug unique, particularly looking for the conversion ratio to choose when switching. Individual response varies remarkably from opioid to opioid, due to asymmetric tolerance, different efficacies, pharmacokinetic profiles, and extra-opioid effects, like an anti-NMDA effect, although the clinical ‘weight’ remains to be established in cancer patients. The correct conversion ratio from morphine to methadone is quite complex and particularly debated in literature. It seems that the previous dose of morphine is determinant in the choice of the following dose of methadone in a proportional way [23, 24]. For example patients taking less than 90 mg of oral morphine, should take $\frac{1}{5}$ of this dose as methadone, patients taking 90–300 mg should take 1/8 of this dose as methadone, and patients taking more than 300 mg should use higher ratio (1:12 or more). However, most of these studies focused on the concept of equi-analgesia, that is patients with adequate pain control presenting adverse effects who were switched and titrated to reach the same level of analgesia. Unfortunately, these concepts are hard to apply in the clinical settings where patients suffer adverse effects from opioids with poor analgesia in most circumstances, a critical condition which requires immediate intervention. The use of these ratios, proportional to the previous dose of morphine, may result in underdosage of methadone in the first days and a slower recovery form the clinical condition for which switching was indicated. Methadone is characterized by a slow onset, due to its large volume of distribution, so that it requires a priming dose to develop an effect to be maintained with subsequent doses. For these reasons a dose of methadone of 1/5 of the previous morphine dose, which could appear high in some circumstances where patients are taking hundreds milligram of morphine, may represent an effective loading dose to be corrected in the following days. In fact, problems related with methadone accumulation occur not immediately, but after 2–3 days. Rotation at risk includes patients on high doses of morphine or those that are highly tolerant, or taking morphine for a long period. Patients on very low doses of opioids mainly do not present relevant problems and can be safely converted using the same methadone-morphine ratio of 1/5 on an outpatient basis [25].

**Adjuvants**

Adjuvants comprehend a wide range of drugs, commonly prescribed to improve opioid analgesia. Antidepressants and anti-epileptics are most frequently administered as co-analgesics in the presence of neuropathic pain, in combination with opioids. Despite the relative efficacy demonstrated by this class of drugs in chronic non-cancer conditions, evidence of the benefit of such combination in cancer pain management is weak. Gabapentin proved to be effective in reducing the mean global score and dysesthesia, but not allodynia, compared to placebo in people with neuropathic cancer pain that is not adequately controlled by systemic opioids [26]. However, magnitude and duration of benefit for patients remains questionable in clinical practice. Similarly, amitryptiline added to opioids was able to reduce the worst pain only, while producing more central adverse effects, in comparison to patients receiving opioids alone [27].

Corticosteroids are widely used as co-analgesic for different pain syndromes however further randomized studies are warrant to better define their role [28]. The role of adjuvants remains poorly defined, at least in advanced cancer patients receiving opioids, and requires further data from well designed and robust studies. In particular, the timing of starting these drugs, potentially they should be started at the first step when non-opioid analgesics, considered poorly effective for neuropathic pain are given first.

**Conclusion**

The WHO method remains of paramount importance and should continued to be encouraged when approaching advanced cancer patients with pain, for the high chances of success, ranging between 70 and 90%. Despite the lack of strong evidence to produce unbiased estimates of the proportion of patients in whom the ladder produces satisfactory results and the fact that no controlled studies with other methods have been conducted to assess its validity, there is the risk to underestimate the educational meaning of this simple approach. Although these guidelines can be implemented, currently the correct use of the WHO method can lead to adequate long-term pain control in most patients with advanced cancer disease.

**References**