Special Report
WORLD HEALTH ORGANIZATION GUIDELINES:
PROBLEM AREAS IN CANCER PAIN MANAGEMENT

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Introduction

Pain is a prevalent symptom experienced by at least 30% of patients undergoing an oncologic treatment for metastatic disease and by more than 70% of patients with advanced cancer. Although cancer pain cannot always be entirely eliminated, appropriate use of simple therapies can effectively relieve pain in the majority of patients. In 1986, the World Health Organization (WHO) published guidelines for cancer pain management based on the three-step analgesic ladder. These steps comprise a sequential approach according to the individual pain intensity, which begins with non-opioid analgesics and progresses to opioids for moderate pain and then for severe pain. Step I includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and other non-opioid drugs for mild and moderate pain. An opioid should be added to the NSAID if pain persists or increases, if intolerable adverse effects are encountered, or if pain is moderate to severe at the outset. Opioids conventionally used for moderate pain constitute the second analgesic ladder. If pain continues unrelieved or is severe at the outset, opioids of higher potency should be used.

Adjuvant drugs are regularly used in all steps according to the individual needs (Table 1). The essential concepts in the WHO approach include the use of drugs by mouth, by the clock, and by the ladder. Individual flexibility and attention to details are strongly recommended. Physicians should also take into account the individual response to analgesics as well as the possible occurrence of adverse effects and then treat the patient appropriately. Medication should be administered by the least invasive and most convenient route available to provide the patient with adequate analgesia. In the presence of persistent pain, medication should be administered around-the-clock. Attention should be paid to the individual response of patients, and a continuous pain assessment is recommended. Regular monitoring for possible adverse effects, as well as treating these adverse effects if they occur, is mandatory.

Table 1. — Three-step Analgesic Ladder*

<table>
<thead>
<tr>
<th>Step</th>
<th>Pain</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Moderate to severe pain</td>
<td>Non-opioids plus strong opioids</td>
</tr>
<tr>
<td>II</td>
<td>Mild to moderate pain</td>
<td>Non-opioids plus opioids for moderate pain</td>
</tr>
<tr>
<td>III</td>
<td>Mild pain</td>
<td>Non-opioids</td>
</tr>
</tbody>
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In each step, adjuvants should be prescribed according to the clinical situations.

The feasibility and efficacy of the analgesic ladder have been reported in various studies. However, cancer pain is still undertreated, despite the availability of potentially effective therapy. In a study by Cleeland et al., only approximately 40% of patients received an appropriate treatment. Barriers to cancer pain management are listed in Table 2. Unrelieved pain can have a negative impact on the quality of the patient’s physical, psychological, social, and spiritual life.

Table 2. — Barriers to Cancer Pain Management

| Problems related to healthcare professionals; inadequate knowledge of pain management. |
| Low priority given to cancer pain treatment; poor assessment of pain or reluctance to report pain. |
| Concern about regulation of controlled substances, restrictive regulations, and availability. |
| Inadequate reimbursement. |
| Fear of patient’s addiction, tolerance, and side effects of opioids; patient’s reluctance to take pain medication. |

The quality of WHO analgesic ladder studies has been recently questioned due to their methodologic limitations, including the circumstances during which assessment were made, small sample size, high rate of exclusions and dropout, inadequate follow-up, and lack of comparison with levels of analgesia before the introduction of the analgesic ladder. Controversies exist on the use of Step II of the analgesic ladder proposed by WHO, as no significant differences in pain relief between non-opioids alone and non-opioids plus opioids for moderate pain have been reported. Some analgesics of the analgesic ladder may be more useful for particular pain conditions. A mechanistic approach based on a selective drug administration sequence according to the pain mechanism has been proposed rather than a step-wise fashion based on the overall severity of pain and potency of drugs. 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. Different problems are unresolved due to a lack of controlled studies on the subjects.
These problems include the role of NSAIDs, the prolonged use of NSAIDs in cancer pain, and the utility of Step II. Moreover, 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 remains 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.

The WHO Analgesic Ladder

The largest study on the validation of WHO guidelines for cancer pain relief was conducted over a 10-year period by Zech et al. However, less than half of patients were followed until death. The follow-up was necessarily restricted because both inpatients and outpatients were included. A large proportion of patients (42%) were treated during their hospital stay for oncologic treatments, including chemotherapy, hormonal therapy, radiotherapy, and surgery. Efficacy of pain relief was good in 76%, acceptable in 12%, and inadequate in 12% of patients. Sample choice may have been influenced by selection bias of hospitalized patients referred for the same problem (e.g., difficult pain problems).

No influence of patient selection was present in a recent large survey because patients were referred to the home program for various reasons rather than solely for pain; also, the patient sample was representative of the general population with advanced cancer and was not influenced by specialized referral bias. A low acceptable dropout rate and a minimal time spent for occasional hospital admission were also observed. Almost all of the patients included in this study were considered unfit for oncologic treatment due to their advanced conditions, despite survival similar to those reported by Zech and colleagues, and were continuously followed at home in a similar manner. While approximately 50% had significant pain at referral, only a minority of patients had insufficient pain relief after one week of treatment (22%) and in the last week of life (11%). Severe pain was reported by less than 2% of patients at the study intervals considered. A similar decrease on pain scores was seen during the terminal phase of the illness while maintaining unchanged opioid doses. However, in a recent study, a high-intensity pain was still present in 23.8% of patients in the last week of life. No essential differences were seen when the mechanism of pain was taken into account. Equally effective pain relief could be obtained in all three steps of the analgesic ladder, with over 80% of patients rating their pain as less than moderate regardless of the pain mechanism. These findings limit the hypothesis of a mechanistic approach that is based on the choice of a drug sequence according to the dominant pain mechanism rather than according to the pain intensity and potency of drugs. All the patients who started a mechanistic approach required opioids to achieve an adequate pain relief for both somatic and neuropathic mechanisms of pain. Therefore, opioids are not analgesics for a specific type or cause of pain and should be viewed as agents for specific intensity of pain.

A change from one step to another is usually implemented when analgesia for increasing pain from cancer progression is inadequate or when side effects of the drugs administered become intolerable. The use of these different categories of analgesics can produce adequate pain relief in a few days and can be maintained at a low level of intensity until death.

WHO Step I

The use of NSAIDs may delay the need for escalating opioid doses or may allow the use of lower doses, thus resulting in fewer central nervous system side effects. NSAIDs have been used for prolonged periods or have been introduced in patients on other steps to improve analgesia or to avoid increases in opioid dosage. In a recent report, NSAIDs were suspended due to adverse effects in a minority of cases, and approximately 20% of patients were still taking NSAIDs in the last week of life. NSAIDs have been shown to have a relevant opioid-sparing effect. Their continued use in combination with opioids may explain the relatively low doses of opioids reported. The opioid-sparing effect was equally reported with both somatic and visceral mechanisms. In previous surveys, non-opioid analgesic drugs were administered on 84% and 85% of treatment days either alone or in combination with opioids, for an average duration of 66 days. The duration of Step I of the analgesic ladder ranged from 19 to 42 days (approximately half of the referral-death period) and 19 days. Single-step treatment did not exceed three weeks in more than 50% of patients who started Step I of the analgesic ladder, primarily due to limited survival.

Long-term administration of NSAIDs, used either alone or combined with opioids, has been reported by Ventafridda et al in several patients without noting side effects that are specifically attributable to the use of NSAIDs. However, in another study, passage from Step I to Step II was influenced in 48% of cases due to side effects, which were not specified. It must be recognized that the addition of an NSAID to a therapeutic regimen exposes the patient to the side effects of another medication. However, the broad analgesic effect may optimize the balance between analgesia and side effects in conditions where the increases in opioid dosage would cause opioid-related adverse effects.

The onset of side effects and a ceiling effect suggest that these drugs should be used only for a short time, although they could still maintain their sparing-opioid effect. Caution is needed when using NSAIDs for prolonged periods since long-term studies on NSAID use in cancer pain are lacking. Risk factors such as aging, preexisting renal or gastrointestinal diseases, hypovolemia, or concomitant use of drugs should be considered. Caution is also needed if NSAIDs are administered to patients who are using medications that enhance the toxicity of NSAIDs, such as corticosteroids. Variability in response to individual drugs should be assessed in appropriate multicenter studies that include a large number of patients. Also, effective agents to prevent or limit the adverse effects of NSAIDs should be studied to establish the true role of the prolonged use of these drugs. Prostaglandins appear to prevent to some extent both gastric and duodenal ulcerations that occur in patients who use NSAIDs for at least three months. Indeed, prophylactic treatment with antacids or H2 receptor antagonists did not reduce the risk of serious gastrointestinal complications.

WHO Step II

The role of NSAIDs in the treatment of moderate cancer pain has been questioned recently, and it has been speculated that this step could be bypassed. A meta-analysis conducted by Eisenberg et al reported that no significant differences in pain relief were noted when the use of non-opioids alone was compared to non-opioids plus opioids (also called weak opioids). However, these results were based on single-dose studies or studies involving a small number of patients, and regular clinical use is more effective than would be predicted on data involving single-dose administration. This class of drugs was most frequently used during the treatment, and the drugs were still largely administered in the last week of life. The switch from Step II to morphine was due to increased pain intensity. In opioid-naive patients, a more favorable balance between side effects and analgesia occurred when dextropropoxyphene was administered than when low doses of morphine were used to omit Step II of the analgesic ladder. This supports the view that the traditional WHO method is appropriate and that the drugs in Step II have still an important role. On the other hand, when compared with morphine, opioids for moderate pain are easy to prescribe and are more readily available to patients, especially in some countries (e.g., Italy and Germany). When non-opioid therapy was no longer effective for moderate pain, opioids plus NSAIDs provided adequate pain relief in most opioid-naive patients, and these were used more than 50% of the time during the total opioid treatment. Similar results were reported in other studies, with less than moderate pain occurring in approximately 83% of days with a regimen of weak opioids.

In a study of 871 patients, 24% who were treated by Step II reported a reduction of pain intensity, with a mean duration of 28 days (more than one third of the mean survival time). The most common reason for advancing to Step III was insufficient analgesia, and only 8% of cases were changed because of the side effects. Twenty-four percent of patients benefited from the use of opioids for moderate pain after one month of treatment, although this percentage decreased to 4% after three months.

In a previous study involving 745 home care cancer patients, more than 60% of cancer pain patients who were given opioids for moderate pain maintained an acceptable pain relief until death without requiring strong opioids. The mean duration of Step II of the WHO analgesic ladder was approximately 50% of the duration of total pain treatment. Opioids for moderate pain were largely administered through the course of pain treatment until death.

Step II of the analgesic ladder should be maintained since it allows a soft contact with strong opioids. This approach is also useful in countries with prescription limitations. Moreover, opioids for moderate pain can be administered until death in a large proportion of patients.

WHO Step III

Morphine is the most frequently used opioid in cancer pain management. A wide variation in the mean daily dose has been reported by different centers. The extensive use...
Individualization of therapy has been emphasized to minimize side effects and to improve the opioid response. The individual variability in the response to different opioid analgesics has important implications in clinical practice. The development of adverse effects may limit the use of opioid analgesics and can result in worsened quality of life. A shift from one opioid to another is recommended when the adverse effect/analgiesic 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, it is possible in most cases to not only reduce or relieve the symptoms of opioid toxicity and manage patients who are highly tolerant to previously used opioids, but also improve analgesia and thus the opioid responsiveness. Most patients can achieve adequate pain relief by adjusting drug-related side effects with an aggressive approach, such as changing the route of administration or switching to alternative opioids. Opioid rotation is becoming more prevalent as a means of improving 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 and methadone.

Most patients can continue using oral opioids until death. Subcutaneous administration is the preferred alternate route, while the intravenous route can be used in patients who have already a central vascular access. Subcutaneous administration is commonly used in the last week of life for patients who are experiencing neurological derangement or nausea and vomiting or when an inconvenient analgesia/side effect balance occurs.

Different studies have compared the use of transdermal fentanyl with oral morphine. Although pain control was similar in these studies, a higher use of rescue medication was reported in patients using fentanyl-TTS therapy. Quality of sleep and morning vigilance were improved, and patients experienced less nausea, vomiting, and constipation with fentanyl-TTS. Patients with unstable pain, those who require rapid titration of the analgesic dose, and those who require frequent dose changes are not be the best candidates for this method of analgesia. High dosage is another limiting factor in cachectic and small patients since fentanyl-TTS dosage is limited by the area of application. In patients using more than 2 g of morphine daily, six or eight patches of fentanyl-TTS must be applied on the skin in order to produce a similar analgesia (the maximum patch in Europe is 100 mg/h).

The most common side effects induced by opioid use are constipation, dry mouth, and vomiting. The intensity level of these side effects is acceptable in most patients except those in the last week of life. For these patients, drowsiness and states of confusion frequently occur that are likely due to the metabolic consequences of the end-stage of disease. Therefore, symptom intensity is more likely related to the worsening of the clinical condition rather than to the opioid dosage. A relationship of symptom intensity to the worsening of Eastern Cooperative Oncology Group (ECOG) performance status has been reported. Daily activity was heavily or nearly completely impaired in only 28% of assessed time. Similar findings have also been reported in other experiences.

Adjuvants

Different drugs have been used to improve opioid analgesia. Amitriptyline and carbamazepine are most frequently administered as coanalgesics in the presence of neuropathic pain, and they are administered in combination with opioids. Two reports indicate that one or more coanalgesics were prescribed on 37% of treatment days, most commonly antidepressants, anticonvulsants, and corticosteroids. While adjuvants were prescribed in 35% of patients in the Step I, less than half maintained this kind of medication in Step III. Different rates of coanalgesic use have been reported elsewhere.

In published surveys, the specific role of any drug is difficult to evaluate since these drugs and their dosages were inconsistently reported. Moreover, no controlled study has demonstrated their effectiveness in cancer pain. The possible adverse effects that can occur in the cancer pain population when different classes of drugs are used also should be considered. Anecdotal experience includes gabapentin, baclofen, local anesthetics, and calcium antagonists.

Corticosteroids are frequently used for indications other than coanalgesics, and their role has not been assessed specifically in cancer pain studies. However, in special conditions such as spinal cord compression with bony metastases, they have a relevant role.

Ketamine, an anesthetic agent with N-methyl-D-aspartate (NMDA)-antagonist properties, has been reported to be effective in difficult pain syndromes such as neuropathic pain that is unresponsive to massive doses of opioids. However, because of its adverse effects, routine use of ketamine should be limited to experienced teams.

Other drugs commonly used to limit opioid-related side effects are laxies and antiemetics. These have been prescribed in 69% and 51%, respectively, of the time of morphine therapy. The use of H2 blockers, prostaglandins, sucralfate, and omeprazole in some countries may reflect the consistent use of NSAIDs during the course of the treatment until death. Currently, no clear guidelines exist about the indications of these agents in this context.

Other Treatments

Even when the basic principles for the use of analgesic drugs in cancer pain management are adhered to, approximately 10% of patients experience unrelieved cancer pain or considerable side effects from systemic opioids. Alternatively, rotating opioids or changing the route of opioid administration may still improve the balance of analgesia and adverse effects. Therefore, only a small proportion of patients (less than 2%) with cancer pain are suitable candidates for spinal treatment. These patients are likely to benefit from much smaller doses of morphine and local anesthetics that are injected intrathecally or into the epidural space. Continuous intrathecal administration of a mixture of morphine and bupivacaine is recommended. Patients with neuropathic pain may further benefit from the use of spinal clonidine administration. However, the need for spinal analgesia remains unknown, as the size of the group from which patients are selected for epidural analgesia is rarely reported, and spinal opioids are often started before systemic opioid administration is optimized. Moreover, several issues remain unresolved regarding spinally administered opioids (eg, techniques, delivery systems, modality, the preferable route of administration, conversion problems, the opioid of choice, the best opioid/local anesthetic ratio, the use of spinal adjuvants, adverse effects, technique complications, and problems emerging at home).

The use of nerve-blocking or neurolytic procedures has decreased in the last years. These procedures depend on the expertise of the clinicians involved in cancer pain. Anesthetic blocks and neurolytic blocks have been reported in 8% and 3% of patients, respectively. Only 3.5% of patients required invasive interventions. While 29% of the patients required nerve blocks or neuroablative procedures in the 1980s, a subsequent trend in the decline of these procedures has been reported due to improved drug treatment regimes. It should be emphasized that anesthesiologic techniques are more successful when an appropriate assessment and evaluation of the patient has been made to find the best option prior to performing the procedure.

Conclusions

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. Wider dissemination of the WHO guidelines among health care workers is thus necessary to raise the standard of treatment before introducing additional unvalidated treatments. Many cancer patients still suffer from unrelieved pain due to inappropriate pain management. The physician’s limited experience regarding the management of cancer pain, and the perception of the laws that govern opioid prescription and use.

References


