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Pharmacological management of cancer pain in children

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Abstract

The aim of this review was to assess cancer pain management in children on the basis of research published in the last ten years. Nine were papers providing clinical data, with a minimum of ten patients. No controlled studies were found. Regardless of general principles and existing recommendations, clinical data should confirm the applicability of this concept. The trials published in the last years did not provide further information to improve cancer pain management in children, because of the experience and the low number of drugs used, reflecting only meaningful opinions of experts in the field. The amount and the quality of data still remain poor, as only 737 subjects (about 80 patients per year) were surveyed with open-label designs or retrospective analysis. No comparison among possible treatments or drugs has ever been performed. Most of these trials are short-lived and assessment of adverse effects is often problematic. The experience with opioids is quite limited, and adjuvants have been seldom assessed, unless for case reports which have not been considered in this analysis. The management of breakthrough pain has never been specifically evaluated.

Further clinical trials are needed to evaluate dose equivalence, clinical efficacy and safety of opioid analgesics, differences in opioid response, adjuvants and other drugs commonly used to manage opioid-related adverse effects, and dose strengths necessary for most children.

Keywords: Cancer pain; Children; Pediatrics; Opioids

1. Introduction

Pain in a child with cancer poses significant challenges for health professionals. Pain is the most common discomfort experienced by children with cancer and occurs in almost 89% of patients in an advanced stage of the disease. It is most often not adequately treated because of inexperience and unfounded fears of analgesic treatment [1]. About ten years ago an analysis of scientific literature regarding cancer pain management in children evidenced that existing data were limited and that most recommendations were substantially provided on the basis of anecdotal experience translated by studies in adults [2]. The aim of this review was to assess cancer pain management in children on the basis of research

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published in the subsequent years to appreciate whether more consistent data have been produced to provide more robust data in this population.

2. Research methods

A systematic search of the existing literature from 2004 to December 2013 was performed via electronic database PubMed (http://www.ncbi.nlm.nih.gov) (filter 10 years). The terms were "cancer pain" AND "children" OR "pediatrics". References contained in the article finally selected were reviewed as to the possibility of finding any additional papers of interest. Browsers of pediatric journals were also assessed. For those articles in which the title and/or abstract were not available or were insufficient to clarify the content of the article, the article was read in its entirety to make the decision over its content by the two authors. To be included in this systematic review, papers had to be full text clinical reports studying the pharmacological management of cancer pain in children and published in English language. All clinical study designs were eligible, but case-series with less than 10 patients were not considered. Papers assessing procedural pain and treatment-induced pain were excluded. Non-clinical reports such as reviews were also excluded.

3. Results

The initial search resulted in 61 hits. Title, abstracts or when necessary the full text paper were screened for inclusion. Eight papers met the inclusion criteria. Other five papers were found after checking cross-references or consulting the principal journals of the field (pediatrics, pain, and palliative care). Globally 13 papers in the period taken into consideration provided new clinical data with a minimum of ten patients.

No controlled studies were found. Details of the clinical papers examined are shown in Table 1. Globally, 935 children were surveyed. In six studies [3–8], 706 subjects were treated according the WHO ladder, most of them successfully, with limited and acceptable adverse effects.

Specific drugs have been assessed. In one study transdermal buprenorphine was found to represent an efficient, safe and well tolerated approach to the management of children's chronic cancer pain. Eleven patients (68.75%) responded to transdermal buprenorphine after 2 weeks of treatment. Pain intensity and all outcome measures of global quality of life, including quality of sleep, alimentation, play and activity, speech, and crying significantly improved over the 60-day study period. No severe adverse events were recorded [9]. Good analgesia with high level of satisfaction has been reported in 18 children treated with fentanyl given as patient-controlled analgesia. All children experienced a good degree of analgesia and did not require any other analgesic drug during the treatment. Both subjective and objective parameters improved after starting pain-relieving treatment and no major side effects occurred [10]. In a multicenter study, transdermal fentanyl was found to be a safe and well tolerated alternative to oral opioid treatment. 132 cancer children from a sample of 173 with chronic pain who were previously exposed to opioid therapy were switched to transdermal fentanyl. Pain intensity scores and quality of life items improved, although about 80% of patients discontinued the treatment for a variety of reasons. The treatment for well-tolerated and serious adverse effects was reported in 9.5% of patients [11].

Two retrospective studies assessed the effects of opioid switching. In a series of seventeen patients switched to methadone, there was an improvement in analgesia with 16 patients remaining on methadone therapy until death for a median of 36 days [12]. Twenty-two children (14%) on opioid therapy underwent 30 opioid rotations. The opioid was substituted either for excessive side effects or inadequate analgesia. Five patients (23%) required two rotations, 3 during the same admission. Adverse opioid effects improved in 90% of cases, and all failures occurred when morphine was rotated to fentanyl. There was no significant loss of pain control or increase in mean morphine equivalent dose requirements [13].

One series reported about the effectiveness of ketamine in children receiving high doses of opioids. Subanesthetic doses of ketamine were used to treat 11 children who were on high doses of opioids and had uncontrolled cancer pain. In 8 of 11 patients, ketamine appeared to improve pain control and to have an opioid-sparing effect [14].

Data regarding interventional procedures were limited. One retrospective analysis of a small series assessed the use of epidural and peripheral nerve blocks in very advanced cancer children. Pain scores improved in nine cases in 1–5 days. A continuous catheter-delivered pain blockade contributed to analgesia, moderated opioid requirements, and did not preclude death at home [15].

4. Discussion

Despite increasing awareness about causes and treatment of pain in children, most of them with advanced illness still experience pain and receive suboptimal pain control [1]. The World Health Organization documents on cancer pain relief and palliative care in children has advocated the global application of the principles of pain management and palliative care for children with cancer. The principles of pain management include the application of the WHO analgesic ladder, appropriate opioid dose escalation, the use of adjuvant analgesics, and the use of non-pharmacological methods of pain control. These principles of pain management should be incorporated into the treatment protocols of all children with cancer, acknowledging that treatment options may be limited for some children [16]. However, regardless of general principles, clinical data should confirm the applicability of this concept and should suggest more specific recommendations particularly in more complex categories. At the moment there is no scientific evidence regarding the strategies to be used for