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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

Table 1
Trials on pharmacological management of cancer pain in children.

Authors	No patients	Setting	Duration days	Drug and dose	Analgesic response	Notes	Tolerability
Ruggiero et al. (2013)	16	Cancer pain	60	Transdermal buprenorphine 8.75–35 μg/h	81.3%	Better quality of sleep, alimentation, play and activity, speech, and crying	Good 93.8% Low tolerance
Geeta et al. (2010)	39	Acute leukemia	NA	WHO ladder	31% on step 1 54% on step 2 15% on step 3	Step 3 analgesia in neuropathic and bone pain.	Constipation
Anghelescu et al. (2010)	14 retrospective	Cancer pain	3–81	11 epidural 3 nerve blocks	12/13 evaluable blocks improved pain control	No preclusion of death at home	None
Mishra et al. (2009)	84	Cancer pain	3 weeks	WHO ladder	Relevant decrease of pain intensity, independently of pain mechanism	82% on step 3 after three weeks	Acceptable number of adverse effects
Hewitt et al. (2008)	185 prospective	Cancer pain	Until death	WHO ladder	NA	Strong opioids 89%, Morphine 75% Mean doses 6.1–29.5 mg/kg Higher doses with solid tumors	Nausea
Davies et al. (2008)	17 retrospective	Cancer pain	Until death Median 36 days	Switched to methadone	Better pain control (94% by parents)	Starting dose 0.1 mg/kg	
Zhen et al. (2007)	139	Cancer pain	NA	WHO ladder	92.8% complete relief	74.8% on step 1 25.2% changing steps	No severe adverse events
Ruggiero et al. (2007)	18	Cancer pain	48 h	Transdermal fentanyl 1 μg/kg/h PCA 1 μg/kg	Good degree of analgesia	High grade of satisfaction	No major adverse effects
Finkel et al. (2007)	11	Cancer pain	1–75 days	Ketamine 0.1–1 mg/kg/h	8/11 patients had a good response	Opioid sparing effect	No psychotropic adverse effects
Zernikov et al. (2006)	124	Mostly pain due to treatment	2265 treatment days	WHO ladder	Effective analgesia with opioids	The mean intravenous morphine equivalence dose was 0.034 mg/kg/h.	Adverse effects were more frequent
Finkel et al. (2005)	132 prospective	Cancer pain mostly leukemia	15 days	Converted from morphine to transdermal fentanyl	86% effective analgesia Reduction of rescue medications	0.98 μg/h/kg to 1.2 μg/h/kg data mixed with non-cancer population	3% withdrawal for adverse effects
Monteiro-Caran et al. (2005)	135	Cancer pain	Mean 34 days	WHO ladder Strong opioids 23%	Satisfactory pain control in 97% of cases	Initial dose of oral morphine 1.8 mg/kg, final dose 7 mg/kg	74% adverse effects Psychological dependence in 2% of patients
Drake et al. (2004)	21 pts	Mucositis 70%	NA	Opioid switching, prevalently from morphine to fentanyl	No loss of analgesia, without increasing opioid doses	Adverse effects resolved in 90% of cases	Adverse effects resolved in 90% of cases

cancer pain management and recommendations are provided on limited experience, with limited number of drugs, reflecting only meaningful opinions of experts in the field. About ten years after a review on the management of cancer pain in children [2], the amount and the quality of data still remain poor, as less than 1000 thousand subjects (about 90 patients per year) were surveyed with open-label designs or retrospective analysis. Other than generic recommendations of WHO ladder, as in adults, it is likely that an individualized treatment may improve the outcome or reduce adverse affects. Of interest, no comparison among possible treatments or drugs has ever been done. Most of these trials are short-lived, or the duration of treatment not clearly explained, 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 and only a study assessed the characteristics of this phenomenon in a small number of patients [17].

Other than the limited evidence of the existing recommendations, several practical points remain unclear and have clinical implications, due to unavailability of some preparations. For example, in pediatric hematology/oncology, pain control by oral long-acting morphine proved to be safe and effective even in the very young patients. The pharmacological properties of long-acting morphine are ideally suited for pediatric use, combining efficacy and compatibility [13], and initial doses of opioids have been suggested, based on the weight of children [11]. However, commercial preparations do not often fit the dose flexibility of opioids requested for children, particularly with slow release preparations or transdermal drugs. Only oral methadone and morphine can be provided as immediate release preparations which can be graduated in a syrup preparation, according to the weight. Alternately, parenteral morphine can be provided in precise doses. Similarly, transdermal opioids have been often reported as effective and non-invasive method for drug administration in children since it avoids discomfort due to intravascular or oral administration. Transdermal opioids represent a useful alternative, because low doses can be tailored according the needs just cutting the new matrix patch, as in most countries low dose strengths are unavailable [10].

Opioid switching may have a positive impact on managing dose-limiting side effects of, or tolerance to, opioid therapy during cancer pain treatment in children. In small retrospective series, this was accomplished without loss of pain control or having to significantly increase the dose of opioid therapy. Despite these encouraging data, this therapeutical approach remains limited to experienced people, due to the lack of prospective data.

Treatments alternative to opioids may be helpful in some circumstances of difficult pain. There are a number of small case series that suggest that ketamine is a useful medication for the control of chronic pain in children. To date, however, there are few data that aid a pediatrician in determining if ketamine is a safe and effective option for children with cancer pain, whose brains are immature and whose metabolism is different from that of adults [18]. Finally, data on invasive procedures remain anecdotal, and precise indications on who should receive such treatments, when these should be performed, and how these should be administered remain unclear.

5. Conclusion

The effective management of pain in pediatric patients with cancer has incalculable benefits to patients, their families, and physicians and nurses. While getting relief from pain for children with cancer may require not just adequate medication but also considerable patient and family education, the treatment with analgesic drugs remains the cornerstone of the therapy [19]. However, information regarding the pharmacological treatment of cancer pain in children is lacking. 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. Unfortunately, the number of children with cancer pain is usually not large enough to support well controlled clinical trials at a single institution. Consequently, multicentre and perhaps multinational efforts are necessary to fully evaluate analgesic strategies for children with cancer pain.

Conflict of interest

No conflict of interest to be declared

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