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# Cancer pain management in children

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The World Health Organization document *Cancer Pain Relief and Palliative Care in Children* (WHO, 1998) advocates 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. 

KEYWORDS: treatment protocols of children with cancer, opioids, analgesics, non-pharmacological methods of pain control.

## INTRODUCTION

Pain is one of the most common and one of the most feared symptoms of children with cancer and their families. If current pain management techniques are utilized the majority of children can achieve adequate analgesia. It is the rare paediatric patient who develops intractable pain. The WHO has established principles of pain management and palliative care as a universal standard of care for all children with cancer. *Cancer Pain Relief and Palliative Care in Children* is a guideline which contains information on the assessment of pain, analgesics and adjuvant analgesics, and the principles of non-pharmacological methods of pain control for painful procedures [WHO, 1998].

## THE EPIDEMIOLOGY OF CANCER PAIN IN CHILDREN

A survey of British and Australian children aged 7–12 years with cancer revealed that approximately one-third had experienced pain in the previous 48 hours. Over half of this group had pain severity in the medium to severe range, and one-third were highly distressed by their experience (Collins *et al.*). Information was acquired about symptom characteristics from a population of children with cancer aged 10–18 years at Memorial Sloan Kettering Cancer Center, New York (Collins *et al*.). Pain was the most prevalent symptom in the inpatient group (84.4%) and was rated as moderate to severe by 86.8% and highly distressing ('quite a bit to very much') by 52.8% of these children. Pain was experienced by 35.1% of the outpatient group, of whom 75% rated it as being moderate to severe and 26.3% rated distress as 'quite a bit to very much'. Although pain is a highly prevalent symptom in children with cancer, its assessment must be considered in the context of highly symptomatic children with complex illnesses.

A study at the National Cancer Institute (Miser *et al*., 1987a) found that 62% of children presented to their practitioners with some sort of pain complaint prior to their diagnosis of cancer. Pain had been present in these children for a median of 74 days before definitive anti-cancer treatment was begun. The duration of pain experienced was not related to the extent of disease. Following initiation of therapy directed at their cancer, the majority of

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children had resolution of their pain, with the rare patient requiring long-term opioid therapy. Children with haematological malignancy had a shorter duration of pain than children with solid tumours (Miser *et al*., 1987a).

As cancer treatment protocols evolve for each patient, treatment-related, rather than tumour-related, causes of pain predominate (Miser *et al*., 1987b; Eliott *et al*., 1991). Causes of treatment-related pain include postoperative pain, mucositis, phantom limb pain, infection, antineoplastic therapy-related pain, and procedure-related pain (e.g. bone marrow aspiration, needle puncture, lumbar puncture, removal of central venous line).

At relapse, or when tumours become resistant to treatment, tumour-related pain frequently recurs. Palliative chemotherapy and radiation may be instituted as methods of pain control in terminal paediatric malignancy, depending on tumour type and sensitivity. Severe pain in terminal paediatric malignancy occurs more commonly in patients with solid tumours metastatic to the central or peripheral nervous system (Collins *et al*., 1995).

A variety of non-malignant chronic pain conditions have been encountered in young adults survivors of childhood cancer (Collins & Berde, 1997). The aetiology of these conditions include causalgia of the lower extremity, phantom limb pain, avascular necrosis, and mechanical pain due to failure of bony union after tumour resection, and rarely post-herpetic neuralgia. Some patients need long-term opioid therapy for the management of non-malignant pain.

## NON-PHARMACOLOGICAL METHODS OF PAIN CONTROL IN CHILDREN WITH CANCER

Non-pharmacological methods of pain control include physical (e.g. heat, cold stimulation, electrical nerve stimulation, acupuncture, massage), behavioural (e.g. relaxation, biofeedback, modelling, desensitization, art and play therapy), or cognitive techniques (e.g. distraction, imagery, thought stopping, hypnosis, music therapy), according to whether the intervention is focused on modifying an individual's sensory perception, behaviours, or thoughts and coping abilities (McGrath, 1991). The decision to use a psychological or pharmacological approach to procedural pain management or both depends on the knowledge of the procedure, the skill of the practitioner, the understanding of the child, and the expectations of pain and anxiety for the particular child undergoing that procedure (Zeltzer *et al*., 1989).

## PHARMACOLOGICAL MANAGEMENT OF CANCER PAIN IN CHILDREN

### Non-opioid analgesics

Acetaminophen is one of the most commonly used non-opioid analgesics in children. Although acetaminophen has a potential for hepatic and renal injury (Sandler *et al*., 1989), this is uncommon in therapeutic doses. The antipyretic action of acetaminophen may be contraindicated in neutropenic patients in whom it is important to monitor fever. Paediatric dosing of acetaminophen is based on the dose-response for antipyretic. Oral dosing of 15 mg/kg every 4 hours is recommended, with a maximum daily dose of 90 mg/kg/day in children and 60 mg/kg/day in younger children. There are no data on the safety of chronic administration of acetaminophen in children.

### Opioid analgesics

Codeine is usually prescribed for moderate pain. In equipotent doses, codeine has a similar analgesic and side-effect profile to morphine. Codeine is often administered in paediatrics in oral doses of 0.5–1 mg/kg every 4 hours for children over 6 months of age. Oxycodone has a higher clearance value and a shorter elimination half life ($t_{1/2}$) in children aged 2–20 years than adults (Poyhia & Seppala, 1994; Pelkonen *et al*., 1973).

Morphine is perhaps the most widely used opioid for moderate to severe cancer pain in children. The major hepatic metabolite of morphine, morphine-6-glucuronide, produces analgesia and side-effects comparable with chronic doses of morphine. Morphine-6-glucuronide may accumulate and result in opioid side-effects in patients with renal insufficiency. Morphine clearance is delayed in the first

1–3 months of life. The half-life of morphine ($t_{1/2}$) changes from 10–20 hours in pre-term infants to 1 to 2 hours in young children (Stanski *et al*., 1978; Olkkola *et al*., 1988). Starting doses in very young infants should be reduced by approximately 25–30% on a per kg basis relative to the dosing recommended for older children. During the neonatal period for term infants, the volume of distribution is linearly related to age and body surface area (McRorie *et al*., 1992; Bhat *et al*., 1990; Pokela *et al*., 1993). A recent study (Hunt *et al*., 2000) suggests that when given an equivalent dose for weight, younger children are likely to have significantly lower plasma morphine and metabolite concentrations. A starting dose for oral morphine of 1.5 to 2 mg/kg/day is recommended for children with pain unrelieved by mild or moderate strength analgesics (Hunt *et al*., 2000).

Oral morphine has a significant first pass metabolism in the liver. An oral to parenteral potency ratio of approximately 3 : 1 is commonly employed during chronic administration (Cherny & Foley, 1996). Typical starting intravenous morphine infusion rates are 0.02–0.03 mg/kg/h beyond the first 3 months of life, and 0.015 mg/kg/h in younger infants. Sustained-release oral preparations of morphine are available for children and are usually administered at twice-daily intervals.

Hydromorphone is an alternative opioid when the dose escalation of morphine is limited by side-effects. Hydromorphone is available for oral, intravenous, subcutaneous, epidural and intrathecal administration. A double-blinded randomized cross-over comparison of morphine with hydromorphone using PCA in children and adolescents with mucositis following bone marrow transplantation showed that hydromorphone was well tolerated and had a potency ratio of approximately 6:1 relative to morphine (Collins *et al*., 1996).

Fentanyl is a synthetic opioid approximately 50–100 times more potent than morphine during acute intravenous administration. Fentanyl has a very rapid onset following intravenous administration, due to its high lipid solubility. The half-life of fentanyl is prolonged in pre-term infants undergoing cardiac surgery (Collins *et al*., 1985), but values comparable with those of adults are reached within the first months of life (Koren *et al*., 1984; 1986; Johnson *et al*., 1984; Gauntlett *et al*., 1988). The clearance of fentanyl is higher in infants and young children than in adults (Johnson *et al*., 1984; Gauntlett *et al*., 1988).

The duration of action of fentanyl following single intravenous bolus administration is much shorter than that for morphine. These features make fentanyl useful for procedures where rapid onset and short duration are important. Fentanyl may also be used for continuous infusion for selected patients with dose-limiting side-effects from morphine. Rapid administration of high doses of intravenous fentanyl may result in chest wall rigidity and severe ventilatory difficulty.

Meperidine is a short half-life synthetic opioid and has been used for procedural and postoperative pain in children. Neonates have a slower elimination of meperidine than children and young infants (Tamsen *et al*., 1982; Hamunen *et al*., 1993; Koska *et al*., 1981; *Pokela et al*., 1992; Mather *et al*., 1975). Normeperidine, a major metabolite of meperidine, can cause central nervous system excitatory effects, including tremors and convulsions (Kaiko *et al*., 1983). This can occur particularly in patients with renal impairment. Meperidine is not generally recommended for children with chronic pain but may be an acceptable alternative opioid for short painful procedures.

Methadone is a synthetic opioid which has a long and variable half-life. The oral : parenteral potency ratio is approximately 2:1. Frequent patient assessment is the key to safe and effective use of methadone. If a patient becomes over-sedated it is recommended to stop dosing, not just reduce the dose, and to observe the patient until alertness is improved. Although ‘as needed’ dosing is discouraged for most patients with cancer pain, some clinicians find this approach a useful way to establish a dosing schedule for methadone (Berde *et al*., 1991).

## ROUTES AND METHODS OF ANALGESIC ADMINISTRATION

Analgesics should be administered to children by the simplest, safest, most effective and least painful route. The oral route of administration of analgesics is therefore the first choice for the majority of patients. Oral dosing is generally predictable,

inexpensive, and does not require invasive procedures or technologies. The intramuscular administration of an opioid is painful, may lead to the under-reporting of pain, and should be avoided. The rectal administration is also discouraged in children with cancer because of concern regarding infection and the great variability of rectal absorption of drugs (Kapelushik *et al*., 1990).

## Opioid dose schedules

Unless painful episodes are truly incidental and unpredictable, analgesics should generally be administered at regular times to provide continuous pain relief. Should breakthrough pain occur 'rescues' are supplemental 'as needed' doses of opioid incorporated into the analgesic regimen. Rescue doses of opioid may be calculated as approximately 5–10% of the total daily opioid requirement and may be administered every hour (Cherny & Foley, 1996).

Opioid dose escalation may be required after opioid administration begins and periodically thereafter. The size of an opioid dose increment may be calculated as follows:

1. If more than approximately six 'rescue' doses of opioid are given in a 24-hour period, then the total daily opioid dose should be increased by the total of opioid given as 'rescue' medication. For example, the hourly average of the total daily rescue opioid should be added to the baseline opioid infusion. An alternative to this method would be to increase the baseline infusion by 50% (Cherny & Foley, 1996).
2. 'Rescue' doses are kept as a proportion of the baseline opioid dose. This dose can be 5–10% of the total daily dose (Cherny & Foley, 1996). An alternative guideline for opioid infusions is between 50–200% of the hourly basal infusion rate (Cherny & Foley, 1996).

## Opioid switching

The usual indication for a switch to an alternative opioid is dose-limiting toxicity. In other words the dose of opioid required to achieve adequate analgesia is limited by opioid side-effects. A favourable change in opioid analgesia to side-effect profile will be experienced if there is less cross-tolerance at the opioid receptors mediating analgesia than at those mediating adverse effects (Portenoy, 1994).

Following long-term opioid dosing, equivalent analgesia may be attained with a dose of a second opioid that is smaller than that calculated from an equianalgesic table (Portenoy, 1997), approximately 50% for short half-life opioids. In contrast to short half-life opioids, the doses of methadone required for equivalent analgesia after switching may be of the order of 10–20% of the equianalgesic dose of the previously used short half-life opioid. A protocol for methadone dose conversion and titration has been reported (Inturrisi *et al*., 1990).

## Opioid side-effects

Children do not necessarily report opioid side-effects voluntarily (e.g. constipation, pruritus, dreams) and should be asked specifically about these problems. An assessment of opioid side-effects is included in an assessment of analgesic effectiveness. All opioids can potentially cause the same constellation of side-effects. If opioid side-effects limit opioid dose escalation, then consideration should be given to an opioid switch. Tolerance to some opioid side-effects (e.g. sedation, nausea and vomiting, pruritus) often develops within the first week of commencement. Children do not develop tolerance to constipation and concurrent treatment with laxatives should be considered.

## Adjuvant analgesics in children with cancer

Adjuvant analgesics are a heterogeneous group of medications that are analgesic in some painful conditions but have a primary indication other than pain (Portenoy, 1993). These drugs are commonly prescribed with primary analgesics. Common classes of these adjuvant agents include antidepressants, anticonvulsants, neuroleptics, psychostimulants, antihistamines, corticosteroids, and centrally-acting skeletal muscle relaxants.

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