

SEVERE PAIN TREATMENT OF CHILDREN IN THE TERMINAL STAGES OF MALIGNANT DISEASES: CASE RAPORT

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Severe pain control is an indispensable and important part of the treatment of children with malignant diseases. The specificity of treatment is connected to the opiate's metabolism, but it is more difficult to estimate pain and there is fear of side effects, which leads to sub-dosing and poor analgesia. The aim of this study is to show that rational use of opiates secures efficient pain suppression in children in the terminal phase of malignant diseases. Oral morphine with fast impact is the gold standard in the initial phase of severe cancer pain therapy and for the treatment of shooting pain in children. Slow release opiates are suitable for long-term use, as they combine efficiency and compatibility. Rotation of fentanyl transdermal allows simpler usage, decreases side-effects and provides good analgesia for children who cannot take opiates orally. Along with an individual estimate of the child's condition, it is important to take care of equi-analgetic doses of opiates and support therapy.

Key words: Palliative Care for Children ■ Pain control

Introduction

Pain is one of the most common symptoms in children with malignant diseases. Pain medication is required by 92% of children with leukemia, 89% with solid tumors and 86% with brain tumors (1). The World Health Organization (WHO) published a guide for cancer pain treatment based on three levels. The third level considers severe pain whose treatment requires strong opiates (2). Unalleviated pain leads to sleeping disorders, tiredness, psychological trauma, and increased morbidity and mortality (3).

Morphine is the medicine of choice for children with severe cancer pain. It metabolizes in the liver, primarily in

morphine-6-glucuronide (10 – 15%) which acts analgetically, as well as morphine-3-glucuronide (50%) with antinociceptive action (4). The half-time of morphine is 2.5 – 3 hours, so the treatment should begin with oral fast-release morphine, along with single doses which are 1/5 of a total daily dose (5). The expected side-effects of morphine (sleepiness, confusion, mouth dryness, urine retention, opstipation) should be prevented as much as possible (6). The other medicine is a synthetic opioid, fentanyl, which is 80 to 100 times stronger than morphine with typical narcotic effects. It has a weaker sedative effect, leads to milder opstipation, and releases less histamine (a gentle hypotensia and itching). The initial fentanyl doses for children, in the form of a transdermal patch, are 12.5 µg/hour every 72 hours (7).

Opioid rotation is replacing an opioid with another one with the aim of increasing the analgetic effect. A better analgetic effect occurs thanks to individual differences in the action of opiates (incomplete cross reaction), the different mechanisms of their action and affinity with the opiates' receptors (9). Individual variability in sensitiveness to opiates is partially connected to the age, sex, body weight, emotional condition, earlier painful experiences as well as genetic polymorphism of µ-opioid receptors. The reasons for opioid rotation are: inadequate analgesia despite dose increase and side effects which cannot be tolerated. It is necessary to know the equianalgetic doses of opiates. The recommended initial dose of the new opioid is 50% of the dose of the previous one. A good analgetic effect is reached in 80% of patients by opioid rotation (10).

Case report

A 15-year-old boy (weight 56.5 kg, height 156 cm) was admitted to the Children's Hospice, Palliative Care Center, University Clinical Cen-

ter, Tuzla in January 2010. From May 2008 he had been treated abroad for Ewing sarcoma on the left hip in a highly differentiated health care institution. A surgical procedure with reduction of tumor mass and osteosynthesis of the femoral head had been performed. He was treated with chemotherapy, along with autologous transplantation of hematopoietic stem cells. Following headaches, nausea and edema of the left front region, in September 2009, through computerized head tomography (CT) and skeleton scintigraphy, the existence of metastatic deposits was confirmed in the head bones of the frontotemporal region on the right side, with infiltration of the meningioma, and it was treated with combined chemo and radiotherapy.

Considering the fact that further oncology treatment was not possible, the patient was admitted to the Palliative Care Center, University Clinical Center Tuzla, for palliative treatment. The dominant symptoms were pain in the left hip, edema, redness of the left leg and headaches. The patient was conscious, communicative, mobile with difficulty but independently, with severe pain while moving the leg (mark 8 on the numeric rating scale for pain measurement). The Karnofsky score at admission was 40%. In the analgetic therapy, along with 40 mg/day slow release morphine sulphate (2 doses per 20 mg), ketoprofen (150 mg/day), paracetamol was also given in single doses of 1g for breakthrough pain. Adjuvant and coanalgetic therapy consisted of dexamethasone (3 mg/day), rantidine (150 mg/day), an anticonvulsive (Seroxat 20 mg/day), a sedative (Lexaurine 3 mg at night) and laxatives (bisacodyl suppositories as needed). Due to leukopenia, trombocitopenia and anemia, granulocyte growth factor, trombocyte concentrate and de leukocytod eritrocites were ordained. Pneumonia was treated with antibiotic therapy.

Due to the inadequate analgetic effect and frequent breakthrough pains, especially at

night, after 5 days of treatment slow release morphine sulfate was replaced with fentanyl transdermal (25 µg/hour) along with single peroral doses of 8 mg morphine hydrochloride at pain breakthrough. Over the next 6 weeks, pain intensity was in the range from 2 to 3 on the numeric scale, while pain breakthroughs were less frequent and connected to physical activity and leg movement. With adequate and continuing health care, the emergence of decubitus was prevented, and by positioning, elevation and leg massage, the increase of edema was prevented. Opistipation was less expressed. The patient's and his family's contentment with the treatment was greater. In time, a close relationship was developed between the patient and his family and the hospital staff.

Two weeks later nurses reported frequent nausea which made oral use of opiates impossible, so along with the fentanyl patch, Voltaren suppositories (2x25 mg/day) were used, while at pain breakthrough single doses of 5 mg morphine hydrochloride were used subcutaneously, Zofran powder 4 mg in the morning (sublingual), and Midazolam (1 mg intravenously) was used for sedation. In the last week of his life, due to more frequent pain breakthroughs, morphine was used subcutaneously 3-4 times a day, and because of the patient's anxiety he was sedated with extra doses of midazolam (3-4 times a day 1 mg).

Discussion

In the advanced phase of a malignant disease, 75-90% of patients suffer pain (11) which shows how underrated cancer pain has been, despite the data from the institutions of palliative medicine from around world that in 95% cases this pain can be controlled efficiently (12). In 70% cases the pain is caused by the malignoma itself and it occurs in the form of nociceptive cancer pain. Malignant cells release algogens: endotelin, prostaglan-

in (E1 i E2), proinflammatory cytokines, P substance, tumor growth factors. Activated nociceptors spontaneously send and create a periphery sensitization, which leads to the activation of N-methyl-D-aspartate (NMDA) receptors, and this results in central sensitization and pain chronification. In about 20% cases the pain is caused by treatment of the malignoma in that surgical intervention can cause nerve damage, chemotherapy releases cytokines that sensitize nociceptors, radiotherapy leads to tissue fibrosis with the compression of nerves, while painful mucositis may be caused by radio and chemotherapy (13). Bony metastasis is one of the most common pain syndromes in patients in the advanced stage of malignant disease. This pain is the consequence of periosteal stretching or a direct compression of a bone nerve, while in 70% cases it is difficult to control. The increased activity of osteoclasts and release of the protein substance related to parathyroid hormones cause hypercalcemia as well as the occurrence of pain breakthrough at movement (14).

The problems estimating pain intensity and the different metabolisms of analgetics make pain treatment in children more difficult (15). Research in the last 15 years has shown that children can be treated safely with pharmacologic analgetic products if attention is paid to the age and dosage according to body weight (16). There are very few valid studies about the treatment of cancer pain in children, considering the fact that there are some significant differences in morphine pharmacokinetics, especially connected to its elimination, which is, it seems, is faster in adults (17). While it was thought that strong opiates are dangerous drugs, completely inappropriate for pain treatment in children, today it is certain that by using them with an adequate titration, as recommended by the WHO, they ensure good pain control in children with malignant diseases (18).

The research, which included 83 children aged from 1 to 19, who were treated for sharp cancer pain with slow release morphine, demonstrates its security and efficiency even in very young patients. This study states that the pharmacologic properties of long acting morphine are ideal for pediatric use, combining efficiency and compatibility (19).

In the study by Geeta et al. (2), sharp pain in 6 out of 39 children with leukemia was treated with morphine sulfate, in six doses of 0.3 mg/kg/per dose. Additional therapy consisted of corticosteroids, antidepressives, oral ketamine, pain breakthrough, and bisacodyl for opstipation prevention. The pain was, thanks to an adequate morphine dose, well controlled, and side effects were insignificant. In our patient, inadequate analgesia by oral morphine sulfate subdosing (40 mg/day or about 0.12 mg/kg/per dose every 4 hours) was corrected after the introduction of fentanyl (25 µg/hour), which corresponds to a greater equianalgetic oral morphine dose (about 0.2 mg/kg/ per dose every 4 hours).

Opioid rotation is not just, on balance, the mathematical conversion of one opiate dose into another, but it requires a serious individual estimate depending on the patient's general condition, comprehensive pain estimates and adjuvant medicine (20). Opioid rotation, as in our patient, is described in a study which consisted of 22 children whose cancer pain was treated with oral morphine. The reasons for opioid rotation were inadequate analgesia (70%), redundant side effects (16.7%) and tolerance development (6.7%). Morphine was most commonly ro-

tated with fentanyl (77%), whereby the side effects were resolved in 90% cases (21).

Continuous monitoring and timely reporting by educated nurses about condition changes in our patient enabled better treatment as well as establishing the trust of the patient and his family. The key factor for rational and efficient pain control, and thereby a reduction in the suffering of the child at the end of his life, as well as support for the family facing a terrible event, as other studies note, is well-educated medical staff (22, 23).

Conclusion

Analgesia is often insufficient in children in the terminal stages of cancer. The most common reasons are fear, lack of experience in prescribing opioids and inadequate adjustment of medicine dose, which mostly leads to sub dosing. For achieving good analgesia constant evaluation and correction of the opiate dose is necessary. Side effects should be prevented or energetically treated, while opiates should be rotated or their application should be changed if analgesia is insufficient, and side effects are noticeable.

Authors' contributions:

Conception and design: SH; Acquisition, analysis and interpretation of data: SH and OS; Drafting the article SH and HT; Revising it critically for important intellectual content: SH and HT.

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