



TREATMENT OF PAIN IN PEDIATRIC PATIENTS

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ABSTRACT:

The article clarifies that pain is a multidimensional phenomenon both in adults and children. The authors reviewed the literature and surveyed the clinical data on the management of pain in pediatric patients. The conclusion was made that pain management in pediatric patients needs adequate management and effective pharmacotherapy with non-opioid and opioid analgesics. Data for pharmacokinetic and pharmacodynamics characteristics of frequently used analgesic drugs are summarized. The authors include useful schemas of pharmacotherapy with nonopioid as well as opioid analgesics and practical guidelines for pain management in clinical ward or outpatient departments.

Key words: pediatric patients, pain management, opioids, non-opioid analgesics, pharmacokinetics, pharmacodynamics

It is well known that “children are not small adults” and this maxim requires from medical professionals the implementation of unconventional approaches among children for the identification, measurement and treatment of pain. Unlike in adults, the nociceptive and antinociceptive mechanisms in children are immature and unformed, the pharmacokinetic and pharmacodynamic characteristics of analgesic medicines are different, the typical emotional and cognitive peculiarities model to a greater degree the manifestations of pain, ranging from first-signal nonverbal reactions in the early stages of the life of the child to emotionally motivated exaggeration or ignoring pain in the next stages of childhood. The next statement shows that for the effective treatment of pain in childhood profound theoretical knowledge as well as significant clinical expertise is needed. A prospective in-hospital study of pain occurrence indicates that 80% of the children admitted for treatment suffered different in nature and intensity pain during hospitalization (Taylor EM, et al. 2008). Similar studies have shown that the children admitted for hospital treatment have been subjected to an unpleasant or painful procedure 2.6 times/day on average, but only 5% of the injections incurred were combined with analgesic drugs (Weingarten K, et al. 2008). There are reports that young children admitted for hospital treatment have been subjected to pain-causing procedures 10 times/day on average, but only 2% of them were treated with analgesic medications (Carbajal E, et al. 2008).

1. Neurobiological characteristics of nociceptive mechanisms in childhood

There is strong evidence that nociceptive mechanisms are functionally active since the earliest stages of development. Clinical observations suggest that defensive reactions to algogenous stimuli appear as early as the late stages of the prenatal period (Finley GA, et al. 2005). During development the morphological structures of a child’s organism are improving, and the physiological mechanisms through which the processes of nociception are realized are enhanced. The position that for the perception of pain completed myelination of the nerves and conscious activity of the cortex is needed has been revised. It is well known that children, born with pronounced hydrocephaly or other pathological conditions accompanied with lacking conscious function of the forebrain’s cortex, perform rudimentary cognitive activity and demonstrate quasi-adequate reaction to algogenous stimuli. Currently, the contention is accepted that prenatal pain exists – the so-called “fetal pain”, and medical professionals should comply with this (Anand KJS, 2006). Such an approach becomes more important by the rapidly increasing repertoire of prenatal diagnosis and surgery. The morphological apparatus needed for pain perception during the period of prenatal development is presented by a functioning subcortical system, including the basal ganglia, the medial and central thalamic nuclei, substantia nigra, the ventral tegmentum zone, kolikuli superior, and midbrain, and the reticular formation in the brain stem. During the last prenatal months thalamocortical mechanisms are super-constructed onto the functions of this system, allowing for nociceptive signaling to be processed at a higher level (Anand, KJS, 2006). Pain in children is a phenomenon depending on complex polymodal interactions in the nervous system, under which the ascending nociceptive impulses triggered by tissue damage, and the endogenous descending antinociceptive mechanisms are modulated by psychological factors much more strongly than in adults. Furthermore, children’s reactions to pain are much more plastic if compared with those of adults, and cognitive, behavioral and emotional components are coming to the fore (Brown SS, et al. 2010). Characteristic for the reactions to algogenous stimuli in childhood are increased excitability and sensitization. After birth, qualitative changes in the functional and morphological parameters of the whole nociceptive system occur. Frequency and conduction velocity are increased and the form of action potentials in the low-threshold A β and high-threshold A δ sensory terminals is amended, gradually narrowing their receptive fields. In newborn infants, A β and

C fibers terminate in the spinal cord into laminae II and I, in contrast to the ones in adult individuals in whom they terminate into laminae IV and III (Brown SS, et al. 2010). The structural organization of the nociceptive system and the insufficient descending antinociceptive mechanisms at birth are the main factors determining the increased sensitivity to algogenous stimuli, and the diffuse and indeterminate spatially positioned location of pain in childhood (Fitzgerald M, Walker SM, 2009).

2. Pharmacokinetic characteristics in childhood

Pharmacokinetic characteristics in childhood differ a lot from those in adults. The absorption rate in children is lower as a result of delayed stomach evacuation due to the decreased gastrointestinal tract tone and motility, the insufficient hepato-biliary production and the reduced blood supply in muscles (Kearns GL, et al, 2003). In accordance with that are clinical observations indicating that in pediatric patients after p.o. administration the absorption of acetaminophen is considerably slower than in adults. By contrast, the percutaneous absorption of analgesic medications in dermal application is increased due to poorly developed corneal layer of the dermis in children. It has been established that in topical application of analgesic unguents with lidocaine, prilocaine or other anesthetics their bioavailability, respectively the risk of systemic toxicity manifestation, are higher (Kearns GL, et al. 2003). The differences in the body composition of children and adults are significant. At birth, the total body liquid is 75% of the body weight in normally born and 95% in premature infants and decreases to 60% during the first five post-natal months. The lower plasma proteins levels in childhood determine the lower degree of bonding, resp. the reduced affinity to medications, and a competitive relationship for binding sites with endogenous substances like lipids, bilirubin etc. Following birth, a gradual increase of adipose tissue and muscle mass starts, accompanied with increase of protein content in the child's body. These pharmacokinetic characteristics may significantly change the effects of medicines with high capacity of binding to plasma proteins and narrow therapeutic range, for example lidocaine (Anderson BJ, Holford NHG, 2007). The capabilities of the organism to metabolise medications are diminished in the postnatal period, due to the insufficient development of the liver enzyme systems. The processes of oxidation, reduction and hydrolysis in phase I, and those of conjugation in phase II of drug metabolism (glucuronidation, sulphonation) after birth take place in different pathways and at different speed. The enzymatic activity of the cytochrome P450 superfamily during the first 3 months after birth is increased, but the activity of enzymes catalyzing phase II reactions increases until the third year after birth (Blake MJ, et al. 2005). In the child's organism, some analgesic medications are eliminated in alternative metabolic pathways, different from those in the adult's organism. It has been demonstrated that in phase II of drug metabolism newborn infants inactivate acetaminophen and morphine not via glucuronidation, as in adults, but by sulfonation reactions (Anderson BJ, Holford NHG. 2007). The insufficient activity of methemoglobin reductase leads to an increased risk

of methemoglobinemia after the application of local anesthetics (lidocaine, prilocaine) in young children. The reduced renal blood flow during the first years after birth results in a lower rate of glomerular filtration and reduced tubular secretion, manifested by lowered renal clearance of medicines. With growing up, the effectiveness of metabolic processes increases and at the age of 10 it is already equal to the one of adults. The relative metabolic efficiency of children is better and therefore requires that the dosage of analgesic medications in pre-puberty be higher (Kearns GL, et al. 2003). There are no uniform guidelines for the application of opioid analgesics in breastfeeding and early age. It is assumed cautiously, that in childhood lipophilic opioids (fentanyl) may be more effective (Tibboel D, et al. 2005).

3. Pharmacodynamics of analgesic medications in children

Opioid analgetics

Morphine: The application of morphine in pediatric practice is considered as the "gold standard" for intra-operative or post-operative analgesia of children with acute or chronic pain. The medicinal product has a low price, routine use in specialized hospitals and widely accepted pharmacotherapeutic guidelines, trivial implementation methods and the profile of adverse reactions is very well investigated. In childhood, morphine is most often administered in a "bolus" dose, by continuous infusion or in procedures of patient-controlled analgesia (PCA). *Fentanyl:* The medicinal product is a synthetic opioid peptide, with 75-100 times stronger analgesic effect than morphine in intravenous administration. In intravenous infusions, fentanyl is the most commonly used for peri-operative analgesia opioid analgesic. In 1991, a pharmaceutical formulation for transdermal administration (TF) was created, enabling continuous, noninvasive and controlled release of fentanyl. Clinical data from studies in children indicate that TF is a medicinal product excelling morphine, with a really good analgesic effect and minimum side effects (Noyes M, Irving N. 2001). Another medicinal product with a really good analgesic effect in pediatric patients is *Feptanyl citrate* for peroral transmucosal administration (OMF). This pharmaceutical formulation is very suitable for children because it is easy and pleasant for administration and the analgesia onset is fast. Children prefer OMF over Oxycodone because of its organoleptic and analgesic qualities, that's why it is very suitable for non-hospital use in childhood (Dsidá RM, et al. 1998). When used for premedication in painful interventions, OMF provides high serum levels over wide intervals - 53 ± 40 min (Wheeler M, et al. 2002), which impedes the precise estimate of the moment to start the intervention. *Tramadol:* The pharmacotherapeutic profile of tramadol is similar to that of codeine, but considerably fewer side effects such as respiratory depression and constipation have been observed. The medicinal product is well tolerated in pediatric patients and can be used with priority over other opioid analgetics for treatment of moderate to severe pain in patients with cardiovascular, renal or hepatic problems (Bozkurt R. 2005). Practical guidelines for pharmacotherapy of moderate to severe pain in pediatric

patients with some of the commonly used opioid analgesics are summarized in Table. 1.

Table 1. Dosage and routes of administration of commonly used opioid analgesics in children (Modified by Brown SC, 2010)

Medication	EA dosage (p.e.)	SD dosage (i.v.)	SD dosage (p.o./t.d.)	Ratio i.v./p.o.	Effect (time)
Codein	130 mg	NR	1 mg/kg/4 h	-	3–4 h
Fentanyl ^{HT}	100 µg	0.5–2 µg ^{c.i.} /kg/h	12–25 µg	-	72 h
Hydromorphone	2 mg	15–20 µg/2–4 h	40–60 µg/2–4 h	1:2	2–4 h
Meperidine ^{RFS}	75 mg	1.0–1.5mg/kg/3–4 h	1.0–1.5 mg/kg/3–4 h	1:4	1–3 h
Morphine	10 mg	0.05–0.1 mg ^b /kg/2–4 h 0.01–0.04 mg ^{i.} /kg/h	0.2–0.4 mg/kg/4 h	1:2	3–4 h
Oxycodone	5–8 mg	NR	0.1–0.2 mg/kg/3–4 h		3–4 h
Tramadol	100 mg	1.0–.0 mg/kg/4–6 h	1.0–2.0 mg/4–6 h		4–6 h

* EA – equianalgesic, NT – potential toxicity, NR – undesirable, RFS – contraindicated in renal insufficiency and may lead to seizures, SD – initial, b – bolus dose, c.i. – continuous infusion, h – hour, i.v. – intravenous administration, p.e. – parenteral administration, p.o. – oral administration, t.d. – transdermal administration.

Non-opioid analgetics

Non-steroidal anti-inflammatory drugs (NSAID): In infancy, the application of medicinal products from this group is restricted by the possibility of occurrence of toxic effects and the risk of inducing bleeding, kidney damage or exacerbation of an existing bronchial asthma. Prolonged treatment with NSAID may cause gastrointestinal discomfort or, in more severe cases, gastric or duodenal ulcers. Data from clinical studies indicate that treatment of children with rheumatoid arthritis with NSAID cause gastrointestinal discomfort and / or macroscopic lesions in 27% and 43%, respectively (Len C, et al. 1999). In similar studies it has been reported that the risk of exacerbation of asthma or of development of allergic rhinitis is 2-40% (Palmer, J. M., 2005). The risk of side effects is significantly reduced when phar-

macotherapy with these medications is not prolonged. The combination of opioid analgesics with NSAID leads to significant reduction in the dosage of opioids. The application of Aspirin (Acetyl) is contraindicated in childhood due to the potential risk for acute hepatic encephalopathy and lipodystrophy (Reye syndrome) to be induced (Grosser T, et al. 2011).

Acetaminophen (Paracetamol): the medicinal product is the most widely used in childhood non-opioid analgetic for the treatment of acute or chronic pain with mild to moderate intensity. Its combination with opioids or other NSAIDs may enhance the analgesic effect and reduce the required dosage. Practical guidelines for pharmacotherapy of moderate to severe pain with some commonly used NSAID in children are summarized in Table. 2.

Table 2. Dosage and ways of administration of commonly used NSAIDs in children (Modified Brown SS, et al. 2010)

Medication	Dosage	Recommendations
Acetaminophen ^{p.o.}	10–15 mg/kg/4–6 h	75 mg/kg/24 h (75 mg ^{p.r.} /kg/24 h) (4 g/24 h, after the age of 12 years)
Diclofenac ^{p.o.}	1.0 mg/kg/8–12 h	Application is limited in cases of hepatorenal damage, hypertension, edema, retention of liquids calves, gastrointestinal ulceration or bleeding
Ibuprofen ^{p.o.}	5.0–10 mg/kg/12 h	Limitations – such as for Diclofenac
Naproxen	5.0–10 mg/kg /12 h	Limitations – such as for Diclofenac

* h – hour, p.o. – oral administration, p.r. – rectal administration.

Other analgesic medications

Ketamine (Ketalar): The medicinal product is a non-selective antagonist of glutamatergic NMDA receptors inducing the so-called *dissociative anesthesia* (amnesia, seda-

tion, dissociation, analgesia), administered as an adjuvant in anesthesia of adult patients with low risk of cardiorespiratory depression. Unlike its routine use in short term surgical interventions of elderly patients, in children this medi-

nal product is administered considerably less frequently. The excessive salivation and hallucinations induced by the pharmacotherapy with ketamine present substantial limitations of its use in children. *Anticonvulsants*: Medications from this group are the tools of choice for treatment of neuropathic pain. The previously widely administered Carbamazepin has recently been replaced by Gabapentin due to the advantages regarding its adverse reactions profile. In the treatment of children with gabapentin it is necessary to comply with certain limitations determined by its well-manifested sedative action. Current clinical observations indicate that in children a better alternative for the treatment of neuropathic pain is the application of Pregabalin (Maese PJ, et al. 2008). *Anti-*

depressants: The medications from this group are applied as efficient adjuvants in the treatment of neuropathic pain in children. Along with the persistent pain these patients suffer from prolonged sleep disturbances and severe depression. This complicated clinical picture justifies the use of antidepressants as adjuvants. Amitriptyline has proved a suitable medicinal product used as an adjuvant for first-line treatment of chronic neuropathic pain in childhood. The mandatory rule is for the pharmacotherapy to start with careful titration with minimal doses. Practical guidelines for pharmacotherapy of moderate to severe nociceptive or neuropathic pain with some commonly used adjuvant drugs are summarized in Table. 3.

Table 3. Dosage and ways of administration of adjuvant commonly used medication for treatment of nociceptive or neuropathic pain in children (modified, by Brown SC, et al. 2010, Sang SN, Hayes KS, 2006, Watson CPN, et al. 2006)

Medication	Dosage	Indications	Warnings
Ketamine ^{p.o.} Ketamine ^{i.v.}	0.5–2 mg/kg/12 h 0.5–1.0 mg/kg (for 1–2 min) 0.5 mg/kg (for 10 min)	Intraoperative, postoperative pain	Hypersalivation, emergency reactions, tachycardia, hypertension
<i>Anticonvulsants</i>			
Gabapentin ^{p.o.}	5 mg/kg/24 h (titration 3–7 days) 5–10 mg/kg/8 h (subsequent period)	Neuropathic pain, stabbing pain	ADRs: ataxia, disorientation, somnolence, gastrointestinal discomfort
Pregabalin ^{p.o.}	5 mg/kg/8 h	Neuropathic pain	ADRs: such as for Gabapentin
Carbamazepine ^{p.o.}	5 mg/kg/12 h (2–4 weeks) 5–10 mg/kg/8 h (subsequent period)	Neuropathic pain, stabbing pain	ADRs: such as for Gabapentin Monitoring: plasma levels, liver functions, allergic reactions
<i>Antidepressants</i>			
Amitriptyline ^{p.o.}	0.05–2 mg/kg/24 h (titration 3–7 days) 0.1–2 mg/kg/24 h	Neuropathic pain pain in radiation or toxic neuropathy or tumor	Contraindications: neonatal period, children with high cardiopulmonary risk
Doxepin ^{p.o.}	5–10 mg/kg/24 h	Such as for Amitriptyline	Contraindications: such as for Amitriptyline
Nortriptyline ^{p.o.}	2–5 mg/kg/24 h	Such as for Amitriptyline	Contraindications: such as for Amitriptyline

* ADRs – adverse drug reactions, h – hour, i.v. – intravenous administration, p.o. – oral administration

4. Pharmacotherapeutical approaches and criteria for pain management in pediatric patients

For children, pain is an extremely unacceptable somatic psychological problem, which requires pain control by applying different strategies. Treatment should include profound diagnosis and measurement of pain, effective pharmacotherapy by appropriate analgesic and adjuvant medications, adequate dose-regimens, symptomatic treatment of ADRs coupled with appropriate for the age psychological methods. It is acceptable, for the application of pharmacotherapeutic agents to control pain to be based on the “by

the ladder”, “by the clock”, “by the child” and “by the mouth” models. The treatment of pain *by the ladder* depends on two parameters: the intensity of pain in a particular patient and the analgesic characteristics of the discussed medicinal products. There are three levels in the analgesic scale approved WHO: level 1 are the non-opioid analgesics, level 2 are the so-called “weak” opioids, level 3 are the so called “strong” opioids (WHO, 1996). It is accepted that Paracetamol or similar medications are preferred in low to tolerable pain, Codeine, or its analogues, is the tool of choice for moderate to severe pain and Morphine, or its analogues, are pre-

ferred in severe to intolerable pain. In insufficient medication control of pain at a certain level a switch to analgesics from a higher level is needed. The view that strong opioids are contraindicated for children suffering from even severe pain has already been overcome. The treatment of pain *by the clock* is based on the rule that the intervals between the doses should provide an efficient pain control and to prevent the occurrence of episodes with pain. The treatment of pain following the model *by the child* imposes the rule that “there is no dose appropriate for all children,” - the dosage and dose regimens should be customized for each patient. The most convenient and efficient way for application of medicines in pediatric patients is through the mouth. The intravenous application is based on a bolus or continuous infusion through a permanent intravenous port. This approach is considered as the “gold standard” for treatment of children with malignant diseases. In case of episodic pain, the rate of infusion could be increased by 50% (Brown SC, et al. 2010). Intravenous administration of analgesics that is controlled by the patient himself (PCA) provides a rapid, economical, low dose pain relief. PCA is considered as the “gold standard” in pain control with opioid analgesics in children above 5 years, with cancer. The risk of ADRs in PCA with opioid can be minimized by continuous monitoring of the rate of intravenous infusion (JCAHO, 2004).

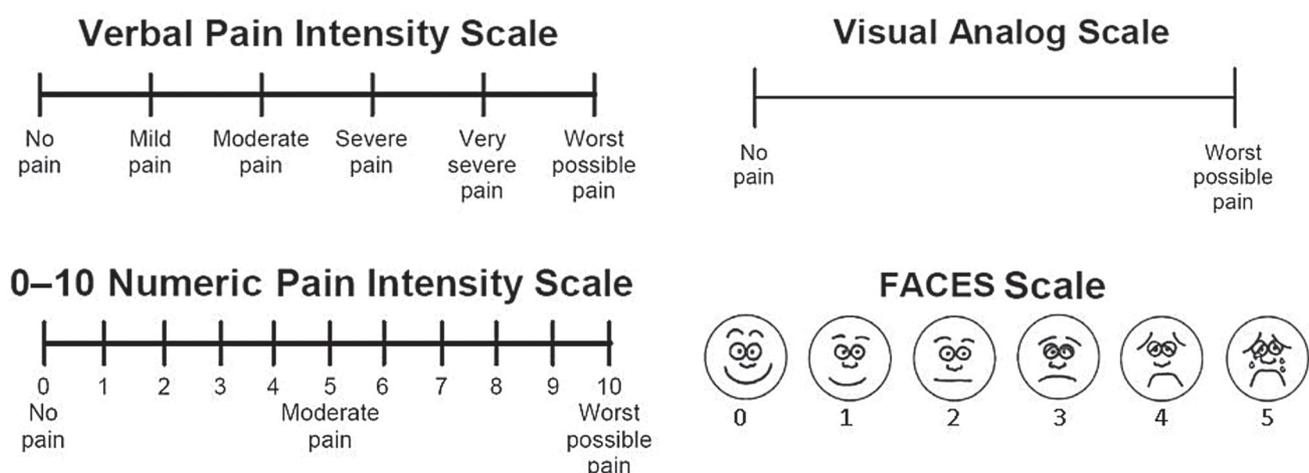
5. Investigation and measurement of pain in childhood

Pain is a personal experience that should be diagnosed and evaluated using methods to verify objectively the nature and the intensity of pain. In childhood three approaches are applied: (i) how the patient evaluates what is being experience (self-evaluation), (ii) how the patient re-

acts to what is being experience (behavior), (iii) what symptoms are manifested during what is being experienced (physiology). These approaches verify the absence or the presence of pain that may affect the quality of life of the patient to different degree: (i) manifestation of functional disorders or disease, (ii) clinical signs of pain, (iii) difficulties in performing routine daily activities, (iv) restriction of social activities and / or restrictions of normal activity (McGrath, R. J., Unruh, A. M., 2006). *Measurement of pain with self-evaluation methods.* These methods are appropriate for patients with sufficiently developed cognitive and verbal abilities. Similarity or difference with previously experienced pain is clarified with direct questions concerning the occurrence, intensity and location of the currently suffered pain, and the type and the intensity of pain are assessed by visual analogue or digital and verbal or nonverbal scales. The visual analogue scale (VAS), used very often in pediatric practice, comprises vertical or horizontal lines of 10 cm length, with 10 verbal or imaging graduations in a continuum from 1 “no pain” to 10 “very severe pain”. VAS is suitable for children above 6 years of age. They are required to determine “*how strong the pain is* “. Many pediatricians prefer the vertically oriented scale (McGrath, P. J., Unruh, A. M., 2006). The visual digital scale contains graduations marked with numbers 1 to 5, 1 to 10 or 1 to 100. This scale is used for older children who understand the meaning of numbers. The verbal pain scale uses descriptions arranged in a continuum “missing, weak, moderate, strong” and is suitable for the age of 4 to 8. The nonverbal imaging scales consist of various facial images which in upward gradation illustrate pains with different intensities, with numerical values 1 to 10 or 1 to 100 (Hicks, C. L., et al., 2001). Models of several types of VAS are presented in Fig. 1.

Figure 1. Models of visual scales used in pediatric practice to determine the pain intensity through self-evaluation

* From top left clockwise: visual verbal scale, visual analogue scale, nonverbal imaging scale, visual digital scale.



Determination of pain through methods for behavior analysis. All patients react to any kind of pain with behavioral changes. The most common reactions accompanying the pain sensation are vocalization, facial expression and body movements. By facial expressions, mimics, body movements and the demand for emotional support, the experienced pediatrician can determine when such reactions are caused by pain and when these are caused by hunger, thirst or anxiety (McGrath, R. J., Unruh, A. M., 2006). In the post-natal period, pain a indication could be the diffuse body movements of in newborns, receding of the painful limb after touch in 6-month-old infants and the defense and rigidity of the painful area in 12-month-old children (Johnston, CC, Strada, M. E., 1986). The child's crying could be a challenge for establishing a correct differential diagnosis of potential pain. Data from pediatric studies indicate that during the first year after birth boys cry more than girls (Grunau, R. V. E., Craig, K. O., 1987). *Determination of pain*

through methods for physiological indicators analysis. Changes of some physiological indicators are not pathognomonic signs of pain, but acceleration of heart rate, decreased peripheral hemoglobin saturation and increased palmar perspiration could be useful for the diagnosis and measurement of acute pain. Changes in these signs are ambivalent and do not essentially contribute to measurement of chronic pain.

Pain is a multidimensional phenomenon both in adults and children. Therefore, the diagnosis and measurement of pain of various etiologies during the neonatal period could be considerably more difficult than in later periods of life. The proposed COMFORT scale for the evaluation of distress/pain by assessing body movements, relaxation, tension of facial musculature, vigilance/attention, respiratory reactions, muscle tone (Ambuel C, et al. 1992) is now widely accepted in micropediatric practice as a reliable diagnostic and prognostic methodology.

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