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REVIEW ARTICLE

Analgesia and sedation in emergency situations and in the pediatric intensive care unit

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Abstract

Objective: To review the current strategies for use of sedatives and analgesics in emergency rooms and intensive care units.

Sources of data: Original data from our emergency rooms and intensive care units; Medline literature review focused on sedatives and analgesic drugs; textbooks.

Summary of the findings: Despite the advances in understanding pain in children, in many critical care units the misguided treatment of pain and anxiety still results in significant morbidity. Difficulties in communication, invasive procedures and the belief that children do not have sufficient neurologic development to process noxious sensations are still a challenge in intensive care units.

Conclusions: The last decade was marked by significant advances in understanding pediatric pain. Treating intensive care unit-related pain and anxiety has clear benefits which may influence the course of disease.

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Introduction

Every child, including preterm newborns, can perceive pain. Some studies show that after 26 weeks' gestation, the peripheral, spinal, and supraspinal pain pathways are sufficiently mature in newborns, allowing them to react to tissue damage by means of autonomic, tissue and hormonal stress responses. It is common knowledge that the experience of pain and the anxiety associated with it cause physical and emotional distress, which may interfere with recovery and even increase mortality.[1-6] Anxiety and fear provoked by the disease or by usual interventions in the pediatric intensive care unit (PICU) and in emergency rooms (ER) may exacerbate pain and the response to stress in critically ill children.[7] Appropriate alleviation of pain and anxiety should be a priority in the treatment of critically ill children. The strategies for improved management of pain and anxiety are reliant on an accurate and timely evaluation of every patient's needs. We should always take into account the patient's

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age, his/her medical history, clinical status, and the type of pain.

Pain and anxiety management strategies

Evaluation of the patient

The evaluation of a PICU patient is quite challenging, since most children are unable to verbalize their pain, fears and anxiety.[8] The severity of pain should be assessed and it is also important to distinguish pain from fear and anxiety so that the adequate medication can be prescribed. Some tools, such as pain scores, are useful in evaluating pain intensity and the level of analgesia and sedation. However, health professionals should rely on their clinical ability, personal judgment and mainly on the family's impressions about the patient's state of health in order to take the right decisions.

Pharmacologically paralyzed children constitute a special group. In these children, pain may develop from an increase in heart rate, or in blood pressure, differences in pupil diameter and lacrimation. Since the proper assessment of pain in these patients is not an easy task, it is recommendable to keep them under excessive sedation and analgesia other than expose them to discomfort and pain.

Pharmacology of the drugs used for pain and anxiety management

The pharmacokinetics and pharmacodynamics of different analgesics and sedatives change with the age and development of children, consequently the doses administered to newborns do not apply to preschool children and adolescents, and vice versa. The absorption, distribution (bioavailability), receptor binding, metabolism and permeability of the drugs to the various organs change considerably during childhood. These differences can result in higher free concentrations of the drug, discrepant volumes of distribution and variation as to drug elimination in different age groups. Comparatively to adults, newborn infants have (proportionally) a higher total body water content, higher extracellular water content, higher blood volume and higher cardiac output, but a significantly lower fat content.[9-11] Furthermore, the drugs pass through the blood-brain barrier more readily in newborns. Although drug metabolism develops quickly, it is low in the first six months of life.

Cytochrome P-450 content is greater in children than in adults, which may be associated with a larger relative liver size in comparison to body weight. This makes the clearance of some medications be higher in pediatric patients; an example of this is the oral administration of morphine, whose dosing interval is shorter for a child, when compared to adult patients.

Renal elimination of drugs is remarkably reduced in newborn infants due to the low renal blood flow and low glomerular filtration rate. There is a quick increase in both during the first three days of life; however, a glomerular filtration rate and a renal tubular function will only resemble those of an adult at about the sixth month of life.[12] For that reason, analgesics and sedatives have to be prescribed with caution for newborns and young children.

Medications

Nonopioids

Midazolam

A water-soluble agent with a rapid onset of action. It is an anxiolytic, inducing rapid sedation and its main advantage is that it causes short-term memory loss. It is four times more powerful than diazepam. Respiratory depression is dose-dependent and hypotension might occur in hypovolemic patients, even with the administration of moderate doses. After the sixth month of life, metabolism is hepatic, similar to that observed in adults.[13] Sedation may have a long-lasting effect due to the accumulation of metabolites in individuals who suffer from obesity, renal insufficiency and hypoalbuminemia. The drug interacts with cimetidine, erythromycin (increases the serum level of midazolam) and theophylline (antagonizes the sedative effect). The conventional IV sedative dose ranges between 0.1 - 0.3 mg/kg, which is efficacious for uncomfortable procedures such as echocardiography and cardioversion. Higher doses (0.4-0.5 mg/kg) may be used in situations that require more relaxation (sedation induction for tracheal intubation) or in quite aggressive procedures. In this case, there is an increased risk for respiratory depression. When midazolam is combined with ketamine for ambulatory procedures, the recommended dose varies from 0.1 to 0.2 mg/kg. The continuous infusion of midazolam (50-500 µg/kg/hour) combined with an opioid (morphine or fentanyl) often results in satisfactory sedation of children submitted to mechanical ventilation. In some cases, the use of midazolam alone can be efficient in this context.[14] Its prolonged use produces tolerance (necessity to escalate the dose in order to obtain the same effect) and abstinence (somatic symptoms such as shivering, crying, tachycardia, sweating, which appear after reduction or cessation of infusion). The modes of administration are oral, sublingual, nasal and intramuscular. When given orally (0.2 to 0.75mg/kg), the drug takes effect within 15 minutes (useful for planned procedures). Nasal administration (0.2 to 0.5 mg/kg) is an adequate option when the intravenous route is not available or when oral administration is not indicated.[15] Patients with immature or abnormal liver function may take longer to eliminate midazolam, which might result in prolonged sedation, delayed weaning from mechanical ventilation, and longer PICU length of stay.

Diazepam

The most widely known and least expensive benzodiazepine. It is slightly soluble in water, being

erratically and incompletely absorbed after IM administration. Hepatic metabolism, with production of two metabolites, one of them with long half-life (20 to 50 hours). Repeated doses of diazepam cause prolonged sedation, which may be good for mechanically ventilated patients. Rapid IV administration may cause respiratory depression and hypotension. A dose of 0.1 mg/kg is appropriate for sedation in slightly uncomfortable procedures. In situations that require stronger sedation, the dose can be escalated to 0.5 mg/kg IV, and repeated at intervals of four or two hours. The maximum oral dose should be 3 mg/kg every 6 hours.

Lorazepam

It has an intermediate half-life between 4 and 8 hours. The peak action is similar to that of diazepam, around one hour; not so useful for acute sedation. Its metabolism is not affected by other drugs. In Brazil, it is only available in tablets. Used for the withdrawal of midazolam in continuous and prolonged use, and for the treatment of tolerance and abstinence. May be used in the dose of 0.05 to 0.1 mg/kg.

Ketamine

Dissociative anesthetic with remarkable analgesic effect and amnestic properties. Although it has an intrinsic negative inotropic effect and vasodilatory properties, ketamine maintains hemodynamic stability due to its secondary sympathetic effects (release of epinephrine and norepinephrine). It has hepatic metabolism (system of microsomal enzymes). Younger children (infants and newborns) have a lower ketamine clearance and longer half-life than older children and adults.[16] Preterm babies and newborn infants have more propensity for postanesthetic apnea.[17] Unpleasant emergent phenomena (hallucinations) occur at a lower frequency in children (3 to 5%) in comparison with adults. The simultaneous administration of a benzodiazepine may help minimize the problem (midazolam 0.1 - 0.2 mg/kg).[18] An IV dose of 1-2 mg/kg is usually appropriate for sedation, with preservation of airway reflexes and respiratory control, allowing for painful procedures (sutures, venous and arterial catheterization, reductions of fractures or luxation) with minimum discomfort. In view of its prolonged analgesic effect, without causing great respiratory problems, it has been used on a large scale in painful procedures in emergency rooms. For deeper sedation, we use a dose between 2 and 4 mg/kg, most times with airway maintenance and mechanical ventilation. For the sedation of mechanically ventilated patients, we use an initial bolus of 10-15 µg/kg/min, with a possible escalation to 40-60 µg/kg/min. Analgesia can be provided with an infusion up to 5 µg/kg/min.[19,20] The concomitant use of glycopyrrolate helps to control the increase of airway secretions, usually observed after ketamine administration. Ketamine is particularly useful as an anesthetic induction agent in severe acute asthma and in patients with cardiovascular instability (shock). The "bronchodilator" dose oscillates between 20 and 40 µg/kg/min. Ketamine can also be used as an adjuvant in opioid and benzodiazepine sedation of children submitted to mechanical ventilation. It is especially contraindicated for patients with intracranial hypertension, as it increases the blood flow in the brain. The prolonged use of ketamine may produce tolerance and abstinence.

Propofol

Very rapid-acting anesthetic used for immediate sedation. Its half-life decreases with age, probably due to better metabolism and increase in the liver blood flow.[21] It has the added advantage of providing rapid sedation. Propofol has been safely used in short-term sedation before painful procedures such as lumbar puncture and cardioversion in patients on spontaneous ventilation.[22] A bolus dose of 1-2 mg/kg, followed by lower intermittent doses, is often efficacious. Doses of 3 to 3.5 mg/kg have been reported; these doses are more effective at obtaining an artificial airway than conventional doses. Temporary hypotension is observed even in hemodynamically stable patients. Propofol was also used for short-term and long-term sedation in pediatric intensive care units.[23] However, the use was suspended due to a possible association with a clinical syndrome that consists of metabolic acidosis, lipemia, heart failure, arrhythmia and cardiac arrest.[24,25] The pathogenesis of this disorder, known as propofol infusion syndrome, remains unclear; however, it has been postulated that a water-soluble metabolite or the use of high doses or prolonged doses might be involved.[26] Not a single case of this syndrome has been found in patients treated with the recommended dose of propofol for a short period of time. Propofol is only recommended for critically ill children, in the PICU, and for a short time at low doses. An infusion lower than 4 mg/kg/hour can be useful in recovering the patient from the sedative effect more rapidly (e.g.: respiratory endoscopy).

Clonidine

Alpha-2 adrenoceptor agonist with remarkable cardiovascular, neurological and neuroendocrine effect, inducing sedation and analgesia.

Rapidly absorbed when given orally, with a half-life of 9-12 hours. It is metabolized in the liver and kidney, and approximately 50% of the dose is passed in the urine in its original form.[27] Preoperative sedation and postoperative analgesia for moderately painful surgeries can be obtained with a single oral dose of 4 mg/kg.[28] The preoperative use of clonidine produces sedation, facilitates the separation of children from their parents, and helps the patient accept a face mask. An intravenous infusion of 0.1-2 µg/kg/hour in combination with low-dose midazolam (50 µg/kg /hour) was effective in producing sedation in ventilated children without any significantly hemodynamic disorder; however,

its formula for intravenous administration is not produced in Brazil.[29] When compared with placebo, the use of clonidine in uncomplicated postoperative treatments allowed for lower doses of opioids. Therefore, it could be used in combination with opioid analgesia in the maintenance of chest drains and in treatments following chest surgeries. The use of clonidine should be considered when conventional therapy with sedatives and analgesics is insufficient or inadequate. Other clinical applications include the management of autonomic seizures observed after severe brain damage and after opioid withdrawal (further details at the end of this chapter).

Thiopental

Powerful anesthetic with several applications in pediatric intensive care. Induces anesthesia in critically ill children, having an immediate action. Hypotension is the main adverse effect of this drug, which should therefore not be used in patients with cardiovascular instability (shock). The conventional anesthetic dose (deep sedation) is approximately 5 mg/kg, which (most times) produces respiratory depression, requiring artificial airway and ventilatory support. Even in patients with a good cardiovascular function, we have used a bolus dose of 2 to 3 mg/kg, due to the risk of hypotension, and if the desired sedation is not achieved, we complete the dose of 5 mg/kg some minutes later. Thiopental is also useful in the management of refractory status epilepticus. Seizures can be controlled with thiopental when anticonvulsants do not reach ideal therapeutic levels. In this case, it is continually infused in the dose of 1-5 mg/kg/hour. In some cases of status epilepticus treated with high doses of thiopental, owing to an increased liver metabolism induced by the chronic use of phenobarbital, patients can efficiently remain in a state of alert and spontaneous ventilation. However, as the drug accumulates (due to its prolonged use) deep sedation and cardiorespiratory involvement might occur. As a general rule, the use of thiopental infusions presupposes the use of vasopressors (epinephrine, norepinephrine or dopamine) and ventilatory support. In patients with obesity or liver involvement, and especially after prolonged use of the drug, there might be long-lasting sedation even after discontinuation of thiopental (redistribution effect).

Chloral hydrate

Efficient hypnotic and sedative agent, with no analgesic effect, which can be given either orally or rectally. The hypnotic dose can be obtained with 40 to 75 mg/kg, with minimal respiratory depression, while the sedative effect can be obtained with smaller doses. The effect lasts for 6 to 8 hours. Even though there is little respiratory involvement, it should never be administered at home, as death has been reported to occur outside the hospital environment. A major drawback of this drug is its slow onset of action, which restricts its use in ERs and ICUs. However, it may be useful as a supplemental sedative agent in children submitted to mechanical ventilation (especially when they develop tolerance to other sedatives) or as a sleep inducer. It may also be used to treat inpatients with pertussis (whooping cough) who have severe coughing fits and cyanosis. Under these circumstances, one should be careful not to oversedate the patient. Chloral hydrate has a cumulative effect, and thus could predispose to bradycardia, deep sedation, and severe respiratory depression. Gastric irritation may be a problem for some children who receive this drug orally; chloral hydrate is contraindicated for patients at risk of developing or who suffer from gastric bleeding. Toxic doses cause respiratory depression and impair cardiac contractility. The drug should also be used cautiously in children with severe bronchospasm.[30]

Opioids

Morphine and its derivatives act on opioid receptors, producing analgesia and sedation without causing memory loss. Therefore, they are often associated with benzodiazepines. Opioids are classified as agonists, antagonists and partial agonists. According to their location in the CNS, opioid receptors are divided into mu, kappa, delta, and sigma. In view of the properties and characteristics of the interaction between opioids and their receptors, the following problems may arise: a) capacity to induce tolerance after some days of administration; b) abstinence as a result of reduction (or abrupt discontinuation) after prolonged use and/or high cumulative doses, c) using an antagonist (e.g.: naloxone) to reverse the side effects (excessive sedation, for instance) produces some reversal of the analgesic effects.

Morphine

Powerful analgesic often used postoperatively in situations associated with severe pain, and in the maintenance of patients on mechanical ventilation. Its pharmacokinetics depends on patient age. In the first month of life, infants cannot eliminate morphine efficiently. Due to this immaturity and to the sensitivity of opioid receptors in the neonatal period, newborns are more susceptible to morphine-induced respiratory depression than adults.[31,32] Around the sixth month of life, the clearance and half-life of morphine (2 to 4 hours) is equivalent to that observed in adults.[31] The active metabolite is eliminated by the kidneys, therefore its effect in patients with renal insufficiency may be extended. It may induce the release of histamine, which is characterized by bronchospasm, hypotension and itching; however, its use is not commonly contraindicated. In our setting, we have avoided the use of morphine in patients with severe cardiovascular instability (shock) and severe bronchospasm. Nevertheless, several centers around the world have used morphine in these situations without relevant harm to the patients. Morphine can be given intravenously, intramuscularly, subcutaneously and orally. Its onset of action after IV administration occurs within 10-15 minutes.

The conventional bolus dose of 0.1 - 0.2 mg/kg, followed by an infusion of 20 - 60 µg/kg/hour, provides patients on spontaneous ventilation with safe pain relief. Newborns and those infants suffering from chronic lung diseases have their protective respiratory reflexes compromised, which increases their risk for respiratory depression. Higher doses can be given to mechanically ventilated children, and should be adjusted according to their clinical response. Newborns who receive opioids should be continuously monitored, preferably through pulse oximetry and in a place that allows quick intervention for airway maintenance, if necessary, as the mere monitoring of respiratory frequency cannot predict apnea.

Fentanyl

A semi-synthetic opioid with rapid onset of action, which, even if given in large doses, does not cause relevant cardiovascular instability. It is a hundredfold more powerful than morphine. The effects of a single dose are determined by the distribution of the drug in peripheral compartments.[33] However, after a long-term infusion, the drug returns to the bloodstream in its original form (redistribution), which increases its half-life by 21 hours.[34] Therefore, infusion should be temporarily discontinued in patients who show signs of excessive sedation in order for the drug to be redistributed and eliminated until a steady state that results in proper sedation and analgesia is achieved, when infusion should be then resumed. The metabolic rate is reliant on the liver blood flow and its elimination is faster in children than in adults; for this reason, pediatric patients tolerate higher doses without suffering respiratory depression. Because of the rapid onset of action of fentanyl, comparatively to morphine under certain circumstances, the effective dose to treat procedural pain is 1-5 µg/kg, however in view of its rapid action, an infusion of 1-10 µg/kg/hour is most times necessary to provide continuous analgesia. Fentanyl is also useful as an anesthetic in patients with labile pulmonary vascular resistance.[35] On the other hand, it does not prevent the increase in pulmonary vascular pressure caused by hypoxia.[36] Infusions of 1-5 µg/kg/hour produce effective sedation in mechanically ventilated newborns. Tolerance to the drug, observed both in newborns and in older children, establishes itself quickly, and an adjustment of the infusion rate might be necessary.[37] In some situations that require long-term analgesia and sedation (e.g.: multiple trauma, burns, etc), we may have to increase infusion by 10 µg/kg/hour in order to offset the tolerance effect. However, it should be highlighted that a cumulative dose greater than 1.5 mg/kg and/or an infusion longer than five days is associated with the likelihood of abstinence in over 50% of the cases.[38] The most dreaded adverse effect is chest wall stiffness that is related to the administered dose (greater than 5 µg/kg) and infusion rate. This effect can be antagonized with the infusion of a muscle relaxant and naloxone. The single infusion of naloxone cannot reverse the situation quickly. Due to its rapid action, fentanyl can also be satisfactorily used for epidural anesthesia. To date, no conclusive studies have confirmed that fentanyl is more appropriate than morphine for pain management in children and newborns; it continues to be a preference of each service, in which the high cost of the medication surely counts.

Meperidine

It is a drug ten times more powerful than morphine. It contains a metabolite that may predispose to seizures when high doses are used (cumulative effect after frequent use). The conventional dose ranges from 1 to 2 mg/kg (IV), with an onset of action slower than that of morphine and a half-life between 3 and 6 hours, sometimes causing decrease in cardiac output, release of histamine, and tachycardia. Given its disadvantages in relation to morphine and fentanyl, the use of meperidine in ERs and PICUs is quite restricted, and should be reserved for cases that show a strong reaction to amphotericin.

Methadone

Opioid used orally and intravenously. It has been increasingly used for the treatment and prevention of abstinence and dependence. The commonly used dose ranges from 0.1 to 0.2 mg/kg every 4 to 6 hours, with a maximum dose of 10 mg/kg. Methadone should be cautiously used since its cumulative effect can produce a longer sedation than desired. In these cases, the dose should be discontinued until the effects wear off, while the interval between the doses should be increased to 8 to 12 hours.

Naloxone

A pure opioid antagonist that prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension through direct competition for mu, kappa and sigma receptors. It does not have any agonist effect and in the absence of opioids it has a small pharmacological activity. It can be given intravenously, intramuscularly, subcutaneously and intratracheally. After parenteral administration, it is quickly distributed into all parts of the body, crossing the blood-brain barrier. The onset of action occurs within two minutes and the duration relies on the dose and route of administration. When given intravenously, its effect lasts from 20 to 60 minutes. In some situations, it is necessary to repeat the dose more than once in order to reverse the effect of opioid therapy, since its action is longer. Under these circumstances, the patient should be monitored for at least two hours. The drug is eliminated by the liver and takes longer in newborns. Every child younger than five years or weighing less than 20 kg, in whom opioid intoxication is suspected, should receive naloxone in the dose of 0.1 mg/kg. Older children should receive 2 mg (according to AAP and the American Heart Association). In neonatal resuscitation, naloxone is indicated for babies

whose mothers received opioids in the last four hours before delivery. In rare cases of long-term opioid intoxication, naloxone can be used via the continuous intravenous route.

Other agents

EMLA

A cream containing lidocaine and prilocaine, used to reduce pain associated with percutaneous procedures.[41] It should be applied to the skin 60 minutes beforehand, so it cannot be used in emergency procedures. The systemic absorption of the prilocaine component can lead to subsequent metahemoglobinemia. This is more likely to occur in newborns due to the relative deficiency of metahemoglobin reductase.

Tolerance, dependence and abstinence

For proper management of these three situations it is essential to understand their definitions. Tolerance is the reduction of the drug effect over time, or the need to increase the dose to obtain the same effect. When tolerance occurs, the serum levels of the drug remain the same, but its sedative or analgesic effect is lower. Abstinence is the development of symptoms and physical signs (tachycardia, sweating, agitation, shivering, fever, etc) in response to the sudden withdrawal of the drug or reduction in its dose. Abstinence is mainly related to prolonged use and high cumulative doses. Therefore, patients who develop tolerance are at a greater risk of showing signs of abstinence when the medication is withdrawn. The use of opioids, diazepines and ketamine for short periods and in low doses seldom causes abstinence. Physical dependence is the necessity of the body to continue receiving the drug in order to avoid abstinence symptoms. Tolerance, dependence and abstinence should not restrict the use of sedatives and analgesics in emergency rooms and PICUs, but should be a warning against their unnecessary maintenance in situations that could be treated with other drugs.

Abstinence symptoms caused by opioids, benzodiazepines, barbiturates or ketamine vary as to their presentation and intensity, which means that we should highly suspect of abstinence in children at a greater risk. Symptoms include refusal to eat, salivation, shivering (mild to intense), agitation, insomnia, tachycardia, fever, diarrhea, sweating, hypertonia, dystonic posture and seizures.

The risk of abstinence rises to 50% with the use of fentanyl for longer than five days or with a cumulative dose greater than 1.5 mg/kg; whereas for midazolam, this risk occurs when a total cumulative dose greater than 60 mg/kg is used.[38-40]

Several withdrawal methods exist. In our setting, we have decreased drug therapy gradually down to 50% and then we give an equivalent medication orally in the same dose as continuous medication; six hours afterwards, we decrease the medication by 25%, and six hours after that, we withdraw the IV medication. For the withdrawal of fentanyl, midazolam, and thiopental we use methadone, lorazepam and phenobarbital, respectively. Some centers have used clonidine to treat opioid abstinence in the dose of 3 to 5 mg/kg.

Patient monitoring

Patients admitted to emergency rooms and treated in ICUs with analgesic and/or sedative medication have to be monitored, especially hemodynamically, so that the treatment strategy can be planned individually according to the type of disease. ICU patients regularly require tracheal intubation, venipuncture, invasive blood pressure measurement by placement of an arterial catheter, serial exams, and introduction of bladder and gastric probes. In addition to all these invasive procedures that produce pain, discomfort and fear, the equipment constantly connected to the patient such as pulse oximeter and electrodes for cardiac monitoring, are necessary for the control of adverse effects caused by many of the drugs mentioned here, especially those effects related to respiratory depression.

Psychological support

Children who are admitted to a pediatric emergency room or PICU suffer psychological and physical stress, and so do their families. Children's psychosocial needs are quite complex and usually neglected.

The hospital environment, especially intensive care units, is overly illuminated, with constant noise, which interferes with the patient's sleep-wake cycle. In addition to these anxiogenic factors that are peculiar to ICU patients, the families also suffer from anxiety due to the difficulty in communicating with the medical staff and being informed about the clinical outcome and course of the disease. Since the family is a link between the child and the medical staff, it is important that they receive due attention. The family should be told about the necessity to use sedatives and the complications that might arise. It is common knowledge that patients on prolonged sedative and analgesic therapy suffer from abstinence syndrome, in addition to depression and hallucinations after long PICU stays in older children. The patients and their families should be provided with psychiatric support.

Conclusion

The management of pain and the alleviation of anxiety felt by patients while they stay in an ICU should be a highlight in therapeutic strategies. Patients submitted to invasive, uncomfortable and painful procedures should receive medication for alleviation of emotional stress and physical discomfort. To the present time, no consensus exists over which the best sedative and analgesic therapy

should be in the many situations that involve critically ill patients. Studies on the use of sedatives and analgesics in pediatric ICUs have shown that this choice varies on a patient-to-patient basis and according to the pharmacokinetics and pharmacodynamics of the drug, previous experience, economic factors, in addition to local practices and tendencies based on subjective or undefined criteria. The anxiogenic and painful situations PICU patients experience should therefore be valued. These patients should be properly treated and the procedures that cause pain and discomfort should be prevented whenever possible.

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