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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Novel Approaches for Treating Pain in Children

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Abstract
Purpose of Review Good pain management in children, especially those at end of life, is a crucial component of palliative medicine. The current review assesses some of the new and/or innovative ways to manage pain in children. The article focuses on some recent medications/pharmaceutical options such as cannabinoids and also innovative ways to administer medication to children, such as intranasal and inhalation.
Recent Findings Current approaches to pain management now include (1) new uses of old drugs such as ketamine and lidocaine, (2) use of new drugs/medications such as cannabinoids, and (3) creative use of old technology such as atomizers, intranasal drops, and inhalation.
Summary Typically, novel approaches to care rarely start in pediatrics or palliative care. The current review has presented some new and old drugs being utilized in new and old ways.

Keywords Pain · Children · Palliative care · Lidocaine · Magnesium · Clonidine · Dexmedetomidine · Cannabis · 5THC · CBD · Ketamine · Gabapentin · Intranasal · Atomizer · Inhaled

Introduction

Novel issues in medical care can be viewed in two ways. There is the perspective of newest and latest plus there is the alternative view of unusual, special, and unique. We will be reviewing both vantage points in the current article. Also, pain management has many components, such as pain assessment, timing of pain (acute, chronic, sub-acute/prolonged, and at end-of-life), effect of age and disease states on pharmacokinetics and pharmacodynamics of management, pharmacologic and non-pharmacologic approaches to pain, direct-acting medications and co-analgesics, alternative and complementary medicines, and then there is mode of administration. Finally, there is also the concept of total pain concept developed by Dame Cicely Saunders and the importance of treating the whole person when they are suffering.

Pain Assessment

Pain assessment has changed little recently. There are now many tools such as CRIES, NIPS, PIPP, DAN, FACES, CHEOPS, and FLACC that are used to assess pain in children of different ages, disease states, and ethnic backgrounds. All of the tools are constantly being reevaluated and updated with the purpose of increasing validity and/or reliability of the pain measurement tool. Also, new acronyms are being utilized for the updated and modified versions. The key issue is to measure pain as it has been repeatedly demonstrated that the more we measure it, the more probable we will treat and manage the pain.

Basic Pharmacology

There are several articles published monthly assessing the effect of age and/or disease states on the pharmacokinetics and pharmacodynamics of pain medications in children. Each of these articles adds to our knowledge base and needs to be known by those providing healthcare for children in

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specific age groups or specific disease processes, but for the purpose of this article, they are in general not novel in the sense of being special, unique, or unusual.

New Medications

There are many new and special ways to manage pain pharmacologically in children and some of these are discussed below. There also many novel ways for non-pharmacologic management of pain in children and these are not discussed in this review.

With our ongoing opioid crisis, alternative medications and co-analgesics are increasingly important components of pain management. There are many novel options among these analgesics and co-analgesics including lidocaine, magnesium, ketamine, cannabis, clonidine, and gabapentin. Some are discussed below.

Lidocaine is a rather special medication used to manage pain in children. It is a sodium channel blocker that is utilized for intractable pain, for pain that is refractory to opioids or among those for whom there is opioid toxicity or at high risk of opioid toxicity. Lidocaine has a very narrow therapeutic index not unlike many intravenous and inhalation anesthetic agents. Too little and it has little effect and a bit too much, it is at toxic levels, but when it works, it works very well. When it is efficacious, the need for most, if not all other analgesics may be eliminated including high-dose opioids. After a typical intravenous loading dose of around 3–5 mg/kg over 30 min, an intravenous infusion is started at about 1.8 mg/kg/h. In younger children, dosing should be based on body surface area, not weight. Ideally, the healthcare team can readily assess blood serum levels to confirm the drug is in its narrow therapeutic range. If not, patients need to be monitored closely with clinical assessment of supra-therapeutic levels by assessing for tinnitus, oral numbness and metallic taste, and, if progressing, decreased level of consciousness, dizziness, and fatigue, while sub-therapeutic levels will be associated with minimal impact on pain [1–4]. Because monitoring typically includes clinical assessments, many institutions restrict usage to older children, e.g., adolescents/youth. Toxicity, if it occurs, is treated by immediate cessation of the intravenous infusion and the use of antiepileptic medications such as midazolam, if indicated. Some also advocate for the use of 20% of intralipid to bind the lidocaine. Potential contraindications for parenteral lidocaine include heart block, pacemaker dependence, and heart or liver failure.

Another special co-analgesic is intravenous magnesium [5, 6]. Many chronically ill children especially those under palliative care are magnesium depleted. As serum blood levels are poorly correlated with actual body stores, hypomagnesemia is determined after assessing urinary losses, if any, after an oral or intravenous load. Those that are depleted typically have minimal 24 h urinary magnesium after such a load/bolus of magnesium. Intravenous magnesium is typically 50 mg/kg load over 30 min of the sulfate salt. Most oral magnesium supplements cause loose stools, if not diarrhea, so oral magnesium is usually the glycinate salt. The magnesium is well absorbed with this salt and if too much is given loose and/or watery stools develop. Magnesium typically has a co-analgesic effect, i.e., decreases the need for opioids and other analgesics.

Ketamine is used both for analgesia and co-analgesia [7–13]. It is an NMDA receptor antagonist that was primarily developed as an anesthetic induction agent. In addition to its analgesic properties, it can provide sedation, amnesia, and dissociation. Subsequently, it has been observed to have a special role in pain management. It is often added to help in the management of intractable pain or, when high-dose opioid therapy is being utilized, to decrease the dose of opioids and with the decrease in opioids, the risk of an adverse event due to the opioids. Its use may decrease tolerance to opioids and potentially reverse opioid-induced hyperalgesia and allodynia, plus prevent "wind-up" phenomena and neuropathic pain. Typically, low-dose ketamine will markedly decrease opioid requirements and will often result in superior analgesia. It may even reduce phantom pain [14]. Low-dose ketamine, i.e., up to 1 mg/kg/h, is very safe. Alone, it has minimal cardiovascular and respiratory effect and typically has minimal effect on level of consciousness. Side effects are quite uncommon with the use of low-dose ketamine, but nausea and/or vomiting, hallucinations, and/or excessive secretions may occur. Benzodiazepines can be used concomitantly with ketamine in an effort to prevent hallucinations and other psychotropic effects [7]. Patients may experience increased salivation and an anti-sialagogue (e.g., glycopyrrolate) may be necessary.

Cannabis, cannabinoids, and medical marijuana have had a major impact on pain management [15••, 16••, 17]. There are over 200,000 medical users of cannabis in Canada. There are massive numbers of anecdotal reports of success for the treatment of pain and associated symptoms (nausea, vomiting, anxiety, anorexia, insomnia, and muscle spasms) with this class of "medication," but there is much to learn as most products are impure and poorly investigated. As Wong [15••] has aptly stated, there is a "widening gap between accessibility and the evidence for cannabinoids for medical treatment." Although it is used for medical purposes, its primary use is recreational which markedly complicates the objective evaluation of this class of medications. There are over 1000 different strains of cannabis and they produce over 100 active agents, phytocannabinoids. The two main phytocannabinoids are THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol). The potency of the THC is reported by wt% of the dried product and by volume% for oils. Also, the plant has been specifically bred to increase THC concentration in

the dried product, such that, the norm of 3% THC dried cannabis from the 1980s is now 15–30% THC. If the THC content is less than 0.3%, it is classified as hemp. THC is believed to be the primary psychoactive agent in cannabis. THC is associated with many adverse effects including early-onset psychosis and schizophrenia, increased impulse behavior, early-onset and worse bipolar disorder, hallucinations, increased depression, increased suicide, worsening PTSD, and increased MVAs. CBD does not produce a "high" and is considered non-intoxicating. In fact, it is generally accepted that CBD actually counteracts the "high" from THC. The therapeutic effects of both THC and CBD are undergoing marked investigation at this time. Terpenes are the chemicals in cannabis that produces its distinctive odor. There is currently intense interest in medical cannabis, especially among parents of children with pain, especially chronic pain, sub-acute pain, and complex pain modalities, most notably, those receiving palliative care. Cannabis can be administered as a dried bud, edibles, capsules, lozenges, tincture, dermal patch, sprays, and vaporized. Also, it is produced as a pharmaceutical product, such as nabilone and dronabinol. The oils are not very pleasant tasting so are either mixed with foods/syrups to hide the taste or are encapsulated. Cannabinoid receptors, such as CB1 and CB2, are G protein receptors and are present all over the body. Physiologically, they impact on pain, memory, and appetite and they are acted upon endogenously by a variety of endocannabinoids. CB1 receptors are mostly in the brain and modulate appetite, memory, anxiety, body temperature, and aggression. CB1 antagonists decrease appetites and lead to weight loss, but are associated with increased suicide rates. CB2 receptors are mostly peripheral and in the immune system. CB2 agonists are anti-inflammatory and decrease pain. CB2 agonists are present in other plants; for example, cloves contain the CB2 agonist, eugenol, which provides topical pain relief. There is at least a third CB receptor, CB3. Cannabis products are often consider 2nd- to 4th-line products in pain management and typically one starts low and goes slow as it is carefully titrated to effect and to minimize risk of adverse events. Cannabinoids are metabolized through the CYT P450 system, so a variety of medications will alter their metabolism, so wise to check for cross reactions with new medications. There are several recent reviews by Whiting [16••] and Wong [15••] on the medical effects and concerns with cannabis.

Clonidine and similar drugs, such as dexmedetomidine, are increasingly aiding in pain management in children [18–21]. Such drugs have potent and very effective opioid-sparing effect. They are also used to help manage opioid tolerance and withdrawal. Initial doses of clonidine are 1 mcg/kg orally, but can be titrated up to 4 mcg/kg q4h. Clonidine is available in many jurisdictions in an intravenous format and in patch format. It can also be administered intranasally and rectally. Sedation is a common side effect, while respiratory effects are generally minimal. Clonidine has sympatholytic properties and has been used as antihypertensive, so a decrease in blood pressure, as well as decreased heart rate, is expected. If used long term, these drugs need to be withdrawn slowly to minimize risk of rebound cardiovascular effects, especially hypertension.

Gabapentin and similar medications (e.g., pregabalin) are transitioning from the novel to becoming a common if not standard component of analgesia. Initial doses of 3–5 mg/kg are rapidly titrated up to 15 mg/kg qid orally of gabapentin in an attempt to minimize opioid use, if not fully replace it, within many pediatric pain management situations. Side effects, such as sedation, limit its use. But tolerance to the sedating effect is typical, so when sedation becomes an issue, titration rates are decreased to as tolerated escalation of doses. Recent study of the use of gabapentin in the NICU has demonstrated its efficacy among babies with neurologic and gastrointestinal morbidities [22•].

Modes of Administration

Classic ways of administering medications to patients include intravenous, oral, dermal (patches), and subcutaneous routes. More novel approaches are intranasal (including atomizers), rectal, sublingual, buccal, and inhalation.

Atomizers are excellent and are rapidly becoming a popular way of direct administration and thus direct absorption of medication in to the bloodstream in children [23–25, 26•, 27] (https://www.rch.org.au/clinicalguide/guideline_index/Intranasal_fentanyl/). The respiratory region of the nose is very vascular. Molecules of the proper size and in the proper concentration will cross readily in the blood stream and will bypass first-pass metabolism. Also, if the medication contacts the olfactory mucosa, it may bypass the blood-brain barrier and cross directly into the CSF. Factors that affect drug delivery include blood flow, nasal debris, mucous, mucociliary clearance, and nasal first-pass metabolism while drug factors are molecular weight, lipophilicity, pKa, water solubility, and drug formulation. To maximize delivery, the concentration is maximized and thus minimizing the volume and to further minimize the volume per nostril, the dose is divided in half and each half is administered into each nostril. If IN medicine burns, 0.25 ml of 4% lidocaine prior to desired medications decreases burning/discomfort with IN medications. This mode of administration can be used for a variety of medications for variable indications. Opiates may be administered for breakthrough or incident pain. Sedatives can be administered for co-analgesic effect, e.g., for restlessness, agitation, and sedation. Seizures may be managed readily. Alternatively, topical analgesia may be applied prior to nasogastric tube insertion. There are limitations to the use of intranasal medications, and

these include nasal congestion, nasal bleeding, nasal obstruction, dependency on high-flow nasal oxygen, and non-invasive ventilator support. Some medications, such as midazolam, may cause irritation to the nasal mucosa so are not as well tolerated. Prior to administration, the nasal secretions should be minimized. Atomizers have practical concerns. They have a dead space of about 0.1 ml so one needs to add 0.1 ml extra into the syringe prior to administration. Also, volumes that exceed 0.5 ml (0.1 ml for neonates) are usually divided in to 2 doses with administration into each nostril of each half of the dose. Thus, a 0.2-ml dose in a neonate will require 0.3 ml of medications to address dead space and need to divide the dose in two parts of one dose of 0.1 ml/nostril. Ketamine doses for intranasal use in children range from 0.5 to 6 mg/kg and one observes analgesia initially and sedation at higher doses. The addition of midazolam 0.2 mg/kg leads to increased sedation and decreased ketamine dose. Dexmedetomidine peaks in 10–20 min with doses of 0.5–2. 0 mcg/kg. It is also well-tolerated, i.e., minimally irritating and minimal respiratory effects, but may cause hypotension or bradycardia. Fentanyl doses of 1–2 mcg/kg are effective and provide rapid and acute relief of pain. Pieper et al. [26•] recently presented the efficacy of intranasal fentanyl for respiratory distress in children followed by palliative medicine. This approach can be readily applied to children for pain. Foster et al. [27] utilized intranasal fentanyl for post-operative pain in adults and demonstrated an 85% bioavailability. Initial dose of intranasal fentanyl is about 1.5 mcg/kg and can be repeated as needed about 10 min later.

Inhalation of medication is an effective but uncommon route for non-gaseous medication administration [28–30]. Many medications can be effectively and rapidly absorbed through the bronchial tree. The mode of administration needs to be carefully planned. Ideally, the inhaler is hand held and provides accurate doses, and the particle size within the aerosol is selected to optimize delivery and absorption of the active agent at the bronchial tree. Worsley et al. [31] in 1990 demonstrated that fentanyl may be readily administered by aerosol for post-operative pain. Subsequently, MacLeod et al. [30] presented in 2012 their evaluation of fentanyl inhaler (25-mcg doses) and noted that the study device performed similar to a 25-mcg intravenous bolus. While inhaled fentanyl is readily absorbed and effective for pain management, morphine is not. Morphine when inhaled is effective for dyspnea, but has poor analgesic effects. But this may be due particle size and mode of administration as described next. Krajnik [28] presented a nice review of the theory and practical aspects of administering nebulized medications. It is important to have a standardized approach to the inhalation method. One needs to know where are the receptors in the lungs that you wish your medication to act at, and will the aerosolized medications actually reach these receptors. Alternatively, if not acting at receptors in the lungs, will the medication actually be absorbed in the pulmonary vasculature and act systemically or will the medication be rapidly metabolized in the lung and have minimal systemic impact. Almost 50% of nebulized medications are trapped in the chamber, and a further 25% is lost in expiration. Different systems inject particles of specific sizes in to the inspiratory stream at different times to facilitate delivery to specific areas of the lung. Also, ideally, the injected particles are injected early to mid-inspiration with the end of inspiration used to "push" the medication into the lungs. With this system, there is no administration during the expiratory phase. To further complex matters, is the patient's own inherent breathing pattern. A breathless cancer patients breaths much differently than a healthy young adult, so each patient would be expected to need an inhaled administration plan to match them. Alternatives are vaporization administration, e.g., as noted earlier, cannabis is often inhaled after vaporization.

Conclusion

There many novel issues in pain management for children within the palliative care context. New medications such as the cannabis derivatives are early in to clinical practice, while older medications such as lidocaine, ketamine, clonidine, magnesium, gabapentin, and dexmedetomidine are now finding their niche in pediatric palliative care pain management. Novel approaches to administration of medications include atomizers, intranasal drops, and dose inhalers. All these new tools will invariably improve the care we provide and minimize discomfort in the children we are honored to help care for.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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