**NEWER MODALITIES FOR PAIN MANAGEMENT**

Brenda C. McClain, M.D., DABPM  
*Associated Professor of Anesthesiology and Pediatrics*  
*Yale University School of Medicine*  
*Yale New Haven Children’s Hospital*

**Alpha -2 Agonists**

The alpha -2 agonists used in pain management include clonidine, dexmedetomidine, and tizanidine. There are three adrenoceptor subtypes: \( \alpha_2^A \), \( \alpha_2^B \), and \( \alpha_2^C \). These receptor subtypes are distributed ubiquitously, and each may be uniquely responsible for some of the actions of \( \alpha_2 \) agonists. It is the \( \alpha_2^A \) adrenoceptor that is responsible for the anesthetic and sympatholytic responses. All the subtypes produce cellular action by signaling through a G-protein [1]. G-proteins couple to effector mechanisms, which appear to differ depending on the receptor subtype.

Alpha-2 receptors play a key part in the descending modulation of pain. Descending supraspinal pathways include the periaqueductal gray area of the midbrain, stimulation of which results in widespread analgesia. In particular, stimulation of alpha-2 receptors located in the locus ceruleus and parabrachial nucleus of the medulla affords analgesia through G-protein mediated potassium channel conductance [2].

**Clonidine**

Clonidine, an alpha-2 agonist has been administered by the enteric, neuraxial, and intravenous routes for pain management in various settings of acute and chronic pain. The benefits of clonidine as an adjuvant include 1) reduction in the amount of opioid required for analgesia and thus, a likely decrease in the side effects due to opioids 2) titrated sedation and anxiolysis without additive respiratory depression when given in combination with opioids and 3) vasodilatation and improved circulation of cerebral, coronary and visceral vascular beds.

Topical application (i.e. clonidine patch) has been the most studied mode of delivery. Transdermal use appears to enhance the release of enkephalin-like substances [3], however, it is difficult to employ this modality in the management of acute pain.
McClain, B.C.

Perioperative pain control and sedation have been demonstrated by oral and rectal routes of administration [4,5]. Oral doses of 5 micrograms/kg as a premedicant are often administered with prophylactic doses of atropine to guard against bradycardia. Prospective studies reveal that oral clonidine reduces postoperative shivering, delirium and pain in children [4]. The literature consistently documents appreciable pain control when clonidine is administered by the intravenous and neuraxial routes as an adjuvant to opioid or local anesthetics. [6,7]

Continuous infusion of intravenous clonidine has been cited in the literature as a safe adjuvant for pain control in adult and pediatric populations. The amount of opioids required by patients experiencing procedural pain was reduced by 30%. Hemodynamic stability was maintained within normal limits as patients experienced less than a 10% change in mean blood pressure. [8]. Clonidine has the further advantage of producing sedation that is associated with only small reductions in minute ventilation and no effect on hypercapnic or hypoxic respiratory drives [8,9].

The use of intravenous clonidine infusions in critically ill children has been reported as safe and efficacious without occurrence of complication or need for intervention or support due to sedation, heart rate or blood pressure changes [9].

Perioperative use of intravenous clonidine at 0.5 to 1 microgram/kg/dose has been effective in the management of intractable postoperative pain and in emergence delirium. Hemodynamic stability can be challenged if hydration status is suboptimal or if doses ≥ 2.5 mg/kg are given as an intravenous bolus.

Dexmedetomidine

Dexmedetomidine is an alpha-adrenergic agonist with a greater selectivity for the alpha-2 receptor than clonidine (on the order of 1620:1 versus clonidine's 300:1), which accounts for its linear dose response curve. This allows for a wider dosing regimen than with clonidine, which has a U-shaped dose response curve due to its significant alpha-1 activity at higher doses. Dexmedetomidine has an elimination half-life of two to three hours [10]. Most of the initial clinical evaluations of dexmedetomidine were done in the ICU setting [11,12]. A loading dose of 1 µg/kg followed by an intravenous infusion of 0.2-0.7 µg/kg/hr produces safe and reliable sedation.
McClain, B.C.

Oral dexmedetomidine at 2.5-4.2 μ/kg is an effective premedicant, allowing placement of intravenous cannula in children 4-14 years for procedural sedation. An oral dose of 1 μ/kg appears inadequate [13].

The incidence of perioperative emergence delirium in children from inhalation anesthesia was significantly different for those children receiving intraoperative and postoperative infusions of dexmedetomidine at 0.2 μ/kg/hr. The time to discharge to home from same day surgery was not delayed [14, 15].

Non-invasive and invasive procedures have been successfully performed in pediatric cases with dexmedetomidine. Awake craniotomy and the intraoperative wake up test with dexmedetomidine have been performed with good results, however supplementation with other agents was required [16].

**Tizanidine**

![Tizanidine molecule]

The centrally acting muscle relaxant tizanidine has an imidazoline structure and binds not only to alpha-2 adrenoceptors but also to imidazoline receptors. It is suggested that imidazoline receptors, but not alpha-2 adrenceptors, are involved in the supraspinal inhibitory effects of tizanidine on spinal reflexes [17]. Tizanidine has been used with some success for tension headaches, chronic daily headaches and in the management of analgesic rebound headaches [18,19]. Indications for use in postoperative pain have been suggested, however, tizanidine appears to have a higher drug-drug interaction rate than other alpha-2 agonists [20]. Pediatric uses in cases of spastic quadriplegia have been documented. Doses of 0.1 – 0.2 mg/kg as three times daily in a divided dose has decreased pain and spasticity [21].

Subjects with chronic myofascial pain syndrome (MPS) were titrated up to 12 mg/day of tizanidine over 3 weeks and maintained for 2 weeks. Sleep was assessed via visual analog scale (VAS), pain intensity via short form McGill questionnaire including VAS, disability/level of function, and pressure threshold (tested by algometry) at baseline, weeks 3 and 5, and 1 week after tizanidine was discontinued. Twenty-four subjects completed the study. Pain intensity and disability decreased significantly from baseline at weeks 3 and 5 (P < .001) [22].

Presented at SPA Annual Meeting, 2006
Lofexidine

Lofexidine has not yet received FDA approval. For adult management of opioid withdrawal, clonidine is generally commenced at 0.1 to 0.2mg/dose increasing to a maximum of around 1.0mg/day, and lofexidine at 0.4 to 0.6mg/dose increasing to a maximum of around 2mg/day. Maximal doses are generally administered for only a few days around the time of maximal withdrawal, usually two to four days after cessation of opioids [23]. Doses are then tapered, and ceased seven to ten days after cessation of opioids. The future use of lofexidine may be a consideration in pediatric patients for tapering from prolonged ICU sedation and neonatal opioid withdrawal.

Opioids

Morphine is the gold standard for strong opioids. As the prototype, “morphine equivalents” is the comparative term for converting all opioids into a user friendly language. The half-life of morphine is 114 minutes. Morphine sulfate (MSO4) is metabolized by glucuronidation to M-3 glucuronide which is neutral or possibly antalgic and M-6-glucuronide, an active metabolite with an elimination half-life of 173 minutes [24]. In infants younger than 3 months, the clearance of opioid is 3 to 5 times slower than in adults. Infants at 1-4 days of age showed longer elimination half-lives than the older infants (6.8 vs. 3.9 h). This difference can lead to accumulation and possibly toxic plasma levels with repeated dosing [24, 25]. A small amount of codeine is also formed. Infants older than 3 months of age will metabolize morphine like adults [26].

Decreased responsiveness to opioids may be seen in neuropathic pain due to hyperalgesia where the mechanism of up-regulation of neurokinin-1 and substance P (SP) receptors are implicated [27]. G proteins form a superfamily of essential regulators that signal a myriad of cellular activities including transduction, organization of the cytoskeleton and mu opioid receptor function. Up-regulation of the regulator of G-protein signaling can lead to a decrease of signaling of $G_i/G_o$ coupling of the opioid receptor [28]. This results in both hyperalgesia and decreased responsive to opioids. Hence, neuropathic pain can be associated with reduced opioid anti-nociception. Methadone has seen resurgence due to its NMDA receptor antagonism which reduces opioid tolerance and restores mu receptor activity and analgesia [29]. Escalating morphine requirements can be improved by the institution of methadone [30].
Methadone

Methadone is seen as a second line opioid with a significant risk of toxicity. However, consideration as a first line analgesic is in order since the drug can be effectively employed in acute pain. Opioid tolerance improves with the co-administration of methadone and is only one of its emerging indicated uses. Administration via the oral, intravenous, rectal and neuraxial routes have been used [31].

It is questioned whether IV doses of methadone can provide a longer duration of analgesia than comparable IV doses of morphine. In patients with chronic cancer pain, morphine and methadone given as IV boluses over a five- to six-day period provided comparable durations of analgesia of approximately four hours [32]. Single dose intravenous methadone of 0.1 mg/kg causes greater changes in end-tidal carbon dioxide than with morphine. Intravenous methadone given by reverse PRN scheduling where the dose is determined by the nurse’s Q four hourly assessment is an effective method for postoperative pain management [33]. Intraoperative use of methadone 0.2 mg/kg has shown to decrease postoperative opioid requirements in children [34]. Intraoperative doses of 0.5 mg/kg for major orthopedic surgery with continuation of postoperative Q12 hourly dosing at 0.1 mg/kg/dose appears to hasten time to ambulation, especially after spinal fusion [personal communication].

Oral methadone can be useful for acute pain and is administered on a schedule similar to its intravenous regimens. Oral methadone has been used in hospitalized toddlers less than three years of age. The indication was for the alleviation of pain in those children who experienced severe and persistent pain that was not relieved by nonopioid analgesics [35].
Ketamine, a phencyclidine, has N-methyl-D-aspartate receptor antagonist activity, is known to be analgesic and induces psychomimetic effects. Ketamine’s use in closely monitored settings such as procedural suites, intensive care units and operating rooms have made some institutions reluctant to allow its use on general wards. However, this agent is proving safe in less closely monitored settings and has a wide array of applications.

Intranasal ketamine 5mg/kg with midazolam 0.3 mg/kg provided preoperative sedation and postoperative analgesia in children 5-7 years of age. The onset is similar to oral midazolam, requiring 10-20 minutes for peak effect. Intranasal ketamine was as effective as intranasal sufentanil and midazolam for pediatric dental procedures [36].

Intravenous ketamine has been used in children as young as 2 years of age for procedural sedation. Doses of 1 mg/kg have been used in the management of opioid withdrawal in critically ill children. The underlying principle for use of ketamine for opioid withdrawal is as follows: (1) NMDA receptor antagonists attenuate the occurrence of opioid physical dependence and withdrawal symptoms in adult humans, and (2) (+)-ketamine reduces opioid withdrawal–evoked hyperexcitation in electroencephalographic power spectra in adult humans [37].

Intraoperative low dose ketamine (loading dose 200 μg/kg followed by 5 μg/kg/hr) did not affect postoperative opioid requirements [38]. 20-100 micrograms/kg/hr is administered as a continuous infusion for the management of postoperative and severe medically related pain such as in the treatment of typhlitis [39]. Similar regimens are used in managing sickle cell- related vaso-occlusive crises. Higher doses in the range of 200 μg/kg/hr have been effective in the management of opioid resistant cancer pain.

Mild dysphoria has been reported with prolonged use and the higher dosing range for continuous infusions however, no major adverse effects have been reported in the application of ketamine for acute, severe pain. The use of benzodiazepines does not appear to impact the incidence of dysphoria [40].

Summary

Novel applications of older agents have broadened the armamentarium of pediatric pain specialists and pediatric anesthesiologists. Targeted and titrated delivery of select non-
McClain, B.C.

opioids for antinociception is becoming a reality as more receptor specific agents are devised. More pediatric studies are needed to substantiate the use of the above agents in the perioperative and acute pain settings. Regardless of how creative advancements in pain management may become, patient safety must be first.

References


Presented at SPA Annual Meeting, 2006
expression in a model of neuropathic pain and insensitivity to morphine. JPET. 2003;304:1299-1306.