

The Use of Alpha-2 Agonists in the Pediatric Patient

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ALPHA-2 AGONISTS

PHARMACOLOGY

Adrenergic receptors can be divided into 2 groups alpha and beta. Both of these receptors have subgroups with the alpha receptors being divided into alpha-1 (postsynaptic) and alpha-2 (presynaptic) types. However, alpha-2 adenoreceptors were subsequently discovered both postsynaptically and extrasynaptically. Currently three alpha-2 isoreceptors alpha-2a, alpha-2b and alpha-2c have been defined. The three alpha-2 subtypes bind alpha-2 agonists and antagonists with similar affinities. Alpha-2 adenoreceptors inhibition of neurotransmitter release is mediated through a decrease in calcium ion conductance that involves direct regulation of calcium entry of voltage gated calcium channel ions.¹

Alpha-2 receptors are located throughout the central nervous system (as previously stated) both pre and post synaptically. The afferent terminals are found in the brain stem nuclei and spinal cord. They are located (although to a lesser extent) in the peripheral nervous system in the afferent terminals of peripheral nerves. These alpha-2 agonists presynaptically suppress the release of norepinephrine and other neurotransmitters. This suppression accounts for the circulatory effects and the effects on MAC, pain and sedation.

The locus caeruleus is a small neuronal nucleus located bilaterally in the upper brainstem and is the largest noradrenergic cell group in the brain. It is an important modulator of wakefulness and may be the major site for the hypnotic action of alpha-2 receptor agonists.² The dorsal horn of the spinal cord contains alpha-2a subtype adenoreceptors, whereas the primary sensory neurons contain both alpha-2a and alpha-2c subtypes.

Alpha-2 adenoreceptors are not found in mammalian heart and the bradycardia due to these drugs is a vagomimetic action.

Two alpha-2 agonists are available for clinical use clonidine and dexmedetomidine (as a sedative agent for intensive care patients).

CLONIDINE

Clonidine is a partial agonist with an alpha-2 to alpha-1 selecting ratio of 39. It is available as 100, 250 and 300 ug tablets for oral administration, an injectable solution containing 150 ug/ml for intravenous, intramuscular local and regional use and as a transdermal patch releasing 100, 200 or 300 ug over 24 hours.

Central Nervous System

Oral clonidine has both sedative and anxiolytic properties. Clonidine also confers sedation and anesthetic sparing when given by the neuraxial route.

Cardiovascular System

These drugs decrease blood pressure by decreasing sympathetic outflow from the brainstem, block preganglionic sympathetic neurons in the spinal cord and reset the baroreflex. Clonidine lowers the set point around which arterial blood pressure is modulated. Heart rate decreases by decreasing sympathetic outflow and tone and resetting the baroreflex response, thus decreasing heart rate for a given increase in blood pressure. It also broadens the responses to changes in blood pressure.³ Alpha-2 agonists inhibit SA node firing (via vagal effects) and prolong PR, AV and QT interval. A decrease in cardiac output is the result of activation of postjunctional vascular alpha-2 adrenoreceptors.

Respiratory effects

In dose up to 300 ug clonidine decreases minute ventilation slightly and increases expired carbon dioxide.⁴ It confers no significant effect on hypercapnic or hypoxic ventilatory drive. Children who receive clonidine via the caudal route do not experience depressed respiration.^{5,6}

Renal System

Stimulation of alpha-2 adenoreceptors decreases the secretion of vasopressin and antagonists action on renal tubules.⁷

Analgesia

Alpha-2 agonists may decrease pain by blocking afferent fibers in the peripheral or central nervous system. They also may modulate efferent pain responses from the brainstem. The major effect may be due to the release of substance P in the dorsal horn cells of the spinal cord.

Use in the Pediatric Patient

Premedication

Clonidine is slowly but completely absorbed orally reaching peak concentrations in 60-90 minutes. It can be administered by dissolving the parenteral formulation in apple juice. The elimination half life is 9-12 hours. Half the drug is metabolized in the liver while the remainder is excreted unchanged by the kidneys or feces.

Clonidine given 1.5-2 hs prior to surgery at a dose of 4 ug/kg mixed in apple juice gives adequate sedation children when compared with 0.4 mg/kg of diazepam. Atropine .03 mg/kg was given 60 min prior to the induction of anesthesia to avoid side effects such as bradycardia. It also attenuated the cardiovascular response to intubation in pediatric patients.⁸ This may be especially useful in children at risk for cerebral vascular accidents and cardiac dysrhythmias. Such children would include those with hypertension from renovascular disease or renal failure, those with cerebral arteriovenous malformations or aneurysm and those with myocardial disease or aortic insufficiency. No other serious side effects were observed in this study but the long onset time to sedation was noted. Clonidine 4 ug/kg decreased the halothane requirement needed

to attenuate fluctuations in blood pressure and heart rate from 1.1% to 0.6% in children (45% reduction).⁹

In 90 children age 5-12 undergoing ophthalmic, urologic or otologic surgery, oral clonidine 4 ug/kg given 105 min before induction followed by atropine 0.03 mg/kg 60 min prior to induction showed reduced pain scores and only 33% required rescue medications as compared to 90% of the placebo group in the first 12 hours postoperatively.¹⁰ This may particularly be useful in longer more invasive surgeries to decrease the amount of opioid use and allow patients to be extubated earlier with adequate pain control.

In tonsillectomy patients, oral clonidine 4 ug/kg was compared with midazolam 0.5 mg/kg. The clonidine group exhibited more intense anxiety on separation and during induction. However, the clonidine group had lower mean intraoperative blood pressure, shorter surgery, anesthesia and emergence times and decreased need for supplemental oxygen during recovery. A major problem was that the clonidine group had larger postoperative opioid requirements, pain scores and maximum excitement. Even though discharge readiness, postoperative emesis, and 24 hour analgesic requirements were the same in both groups, midazolam was judged to be better for premedication in tonsillectomy patients. Another disadvantage clonidine must be given 60 minutes prior to induction of anesthesia as compared to 30 minutes for midazolam.¹¹

Clonidine has been shown to decrease the anesthetic requirement for inhalational agents.¹² MAC reducing effects may be due to the effect on central noradrenergic neurotransmission or alpha-2 agonists may themselves be anesthetics. A recent study evaluated the effect of premedication with clonidine 4 ug/kg and the effect on the reduction of MAC of sevoflurane for tracheal intubation in children (MAC_{TI}). The MAC_{TI} was 3.2 in children unpremedicated without the use of N₂O. Adding 60% N₂O but no premedication the MAC_{TI} was 2.4. After clonidine premedication (4 ug/kg orally) the MAC_{TI} without N₂O was 1.9 and with 60% N₂O, 1.4. Therefore premedication with clonidine 4 ug/kg decreased MAC_{TI} by 56% in the presence of 60% N₂O. It must be noted at least 107 minutes after premedication with oral clonidine had elapsed before the induction of anesthesia.¹³

Oral clonidine for premedication may have other side effects. An oral dose of 4 ug/kg has been shown to attenuate the hyperglycemic response to infusion of glucose and surgical stress in children undergoing minor surgery possibly by inhibiting the surgical stress release of catecholamines and cortisol. It failed to suppress the increase in plasma insulin concentration, in response to glucose infusion. However it did not completely prevent hyperglycemia associated with 5% glucose administration. In addition those who received placebo and 0% dextrose infusions responded to surgery with an increase in plasma glucose concentrations but the oral clonidine group did not increase glucose. Patients who were involved in surgeries that lasted 1.7 hours had no problem with hypoglycemia. But if no intraoperative glucose is administered there is a potential risk for hypoglycemia during long operations.¹⁴ Therefore glucose levels must be monitored in longer surgeries.

Nausea and Vomiting

Clonidine 4 ug/kg orally has been shown to have a lower incidence of nausea and vomiting in patients undergoing strabismus surgery, an incidence of only 11%. However in this

study all patients were hospitalized for 2 days after surgery so whether the decrease in nausea and vomiting was due to postoperative restfulness due to the sedation from the clonidine has yet to be determined.¹⁵

Shivering and Delirium

Alpha-2 agonists have been shown to decrease shivering after general anesthesia without decreasing blood pressure or prolonged sedation.¹⁶ Post anesthetic shivering occurs in 5-65% of patients and in addition to discomfort may be associated with hypoxemia, hypercapnia and acidosis. Caudal or intravenous clonidine 3 ug/kg may prevent postop delirium after sevoflurane anesthesia.¹⁷ Even a lower dose of intravenous clonidine 2 ug/kg decreased emergence agitation in children after sevoflurane anesthesia.¹⁸

Controlled Hypotension

Oral clonidine 5 ug/kg the night before surgery and again 90 minutes before surgery was effective for controlled hypotension during maxillofacial surgery. The heart rate and blood pressure during induction and intubation was decreased in the clonidine group. Children who took clonidine required significantly less isoflurane to maintain a mean arterial blood pressure of 60 mm Hg, and less fentanyl and labetalol. They also had a faster recovery and shorter recovery room stay.¹⁹

Epidural Use

Epidural clonidine has been shown to increase the duration of action of caudal analgesia in pediatric patients. The appropriate dose is still being determined. Lee found that clonidine 2 ug/kg added to 0.25% bupivacaine at a dose of 1 ml/kg gave a duration of action of 9.8 hours as compared to caudal bupivacaine alone being 5.2 hours. These patients with clonidine also had a longer duration of sedation 9.1 hours vs. 2.5 hours.²⁰ A recent study by Jamali compared plain bupivacaine 0.25% (1 ml/kg) with bupivacaine 0.25% (1 ml/kg) with 1/200,000 epinephrine or bupivacaine 0.25% (1 ml/kg) with 1 ug/kg of clonidine. Duration of analgesia was 16 hours in the clonidine group, 6 hours in the epinephrine group and 7 1/2 hours in the bupivacaine alone group.²¹

Constant compared a mixture of 1% lidocaine and 0.25% bupivacaine with 1/200,000 epinephrine (total 1 ml/kg) with the same mixture adding either 1 ug/kg fentanyl or 1.5 ug/kg of clonidine. None of the 9 children with clonidine needed any intraoperative narcotic while only 1/9 of the fentanyl and 5/11 of the local anesthetic alone needed intraoperative narcotics. Duration of action till first analgesic was 2 1/2 hours for local anesthetic alone and 3 1/2 hours for the fentanyl or clonidine patients.²²

Caudal studies done with 1% lidocaine (10 mg/kg) with 1/200,000 epinephrine vs. 1% lidocaine (10 mg/kg) with clonidine 3 ug/kg, duration of action was 50% longer in the clonidine group and 3.5 x more patients in the clonidine group had no pain. There were no side effects hemodynamically or with sedation noted.²³

In single shot caudal in children with procedures lasting 90-150 minutes patients receiving either clonidine 1.5 ug/kg or fentanyl 1 ug/kg added to 1 ml/kg of 0.25% bupivacaine with 1/200,000 epinephrine and 1% lidocaine in equal parts had equal efficacy - however the

fentanyl group had undesirable side effects such as vomiting and transient oxygen desaturation. This led the authors to conclude clonidine may be the drug of choice to prolong duration of caudal anesthesia by single injection.²⁴

In combination with ropivacaine for caudal blockade addition of clonidine 2 ug/kg to 0.1% ropivacaine (1 ml/kg) resulted in better postoperative analgesia than 0.2% ropivacaine alone (1 ml/kg). This combination was not associated with any significant degree of sedation or motor blockade.²⁵

In ambulatory inguinal hernia repair patients caudal blockade with 1 ug/kg of clonidine added to bupivacaine 0.25%, 0.75 ml/kg had a significantly longer duration of action (360 min) than bupivacaine alone (346 min) or with 1/200,000 epinephrine (300 min). Also less additional analgesic was used in the first 24 hours at home in the clonidine group. Increasing to 2 ug/kg of clonidine did not increase the duration of action (360 min), but resulted in fewer rescue interventions for pain. Bradycardia and respiratory depression were not observed but a mild hypotension was seen in the clonidine group. Conclusions were made that caudal use of clonidine 2 ug/kg was safe in pediatric ambulatory surgery patients, however patients were kept 6 hours postprocedure.⁵ In ambulatory surgical patients clonidine 1 ug/kg may be the best dose to prolong analgesia and decrease possible side effects such as prolonged sedation.

However, care must be used with caudal clonidine in neonates either term or premature. Two case reports have suggested clonidine may be responsible for apneic episodes in these patients.^{26,27}

For continuous lumbar epidural with 2% lidocaine (8 mg/kg) either 1/200,000 (5 ug/kg) epinephrine or clonidine 2 ug/kg was added. The duration of action was twice as long in the clonidine group as the epinephrine group with no side effects.²⁸

With continuous postoperative lumbar epidural (L4-L5) infusion (in pediatric patients age 1-4 years) after urogenital surgery clonidine, .08-.12 ug/kg/hr added to 0.08% ropivacaine (0.16 mg/kg/hr) gave better postoperative analgesia, increased time to first analgesic demand and reduced total number of doses of supplemental analgesia during the first 48 h after surgery as compared to infusion of ropivacaine 0.1%, 0.2 mg/kg/hr. Analgesia was improved without any signs of increased sedation or other side effects.²⁹

Studies are continuing to determine the optimum dose for the minimal side effects (sedation, hypotension and bradycardia).

Intrathecal

Clonidine 2-3 ug/kg has been added to intrathecal bupivacaine in adults. It may not offer any advantage as far as analgesia but may add more sedation and a greater decrease in blood pressure.³⁰

DEXMEDETOMIDINE

Dexmedetomidine displays specific and selective alpha-2 adrenoreceptor agonism. It is 8 times more specific for alpha-2 adrenoreceptors than clonidine and is currently indicated for

sedation in the intensive care unit. It is currently available for intravenous use only however it has been successfully administered epidurally for postoperative analgesia in humans in clinical trials.

Given as an intravenous infusion at a dose of 1.0 ug/kg for 10 minutes and then 0.2-0.7 ug/kg/hr the distribution half life ($t_{1/2}$) was 9 minutes and elimination half life of 2 hours.³¹

Central Nervous System

This drug causes sedation and anxiolysis. After a loading dose of 1 ug/kg and a maintenance infusion of 0.2-0.7 ug/kg/hr extubated patients required 80% less midazolam than a control group.³² It also decreases the MAC of isoflurane by 90% compared with placebo.³³

Cardiovascular System

Mean arterial blood pressure decreased by 27% and heart rate decreased by 17% in patients receiving a bolus dose of dexmedetomidine 2 ug/kg.³⁴

Respiratory System

In adult males, dexmedetomidine 2.0 ug/kg increases carbon dioxide partial pressure (pCO_2) by 4.2 mm Hg and decreases minute ventilation by 28% with minimal changes in ventilating frequency.³⁵

Analgesia

Dexmedetomidine reduced rescue analgesia (morphine) requirements by 50% compared with placebo in postsurgical patients requiring mechanical ventilation and sedation in the ICU.³²

Use in the Pediatric Patient

Sedation and Anxiolysis in Intubated Patients

Dexmedetomidine infusion has been compared with midazolam infusion for sedation in intubated patients. A dose of 0.25 ug/kg/hr of dexmedetomidine provided equivalent sedation as compared to midazolam at 0.2 mg/kg/hr. The dexmedetomidine group had a lower baseline heart rate when compared to the midazolam group. There was a decreased need for changes in infusion rate and supplemental morphine use with dexmedetomidine. The midazolam group had more episodes of inadequate sedation.³⁶

Two case reports of a 10 week old infant intubated for respiratory failure and a 14 year old adolescent post spinal fusion showed good results with an infusion of 0.25 ug/kg/hr. In the 14 year old patient who had not received sedation a loading bolus of 0.5 ug/kg was administered. Blood pressure and heart rate were lower and morphine needed postoperatively was limited to a single dose. The patient was weaned during continuation of the infusion and extubated 10 minutes after the infusion was discontinued. This shows the drug can be used as a bridge to extubation, decreasing the use of opioids and other sedatives that can cause respiratory depression.³⁷

One caveat must be noted that a 5 week old infant who was receiving digoxin had episodes of severe bradycardia with a dexmedetomidine infusion and so this combination must be used carefully.³⁸

Controlled Hypotension

For spinal instrumentation and fusion a continuous infusion of dexmedetomidine can be combined with isoflurane (0.2-0.3%) in 50% nitrous oxide/oxygen and remifentanyl 0.2-0.3 ug/kg/min. Dexmedetomidine is initiated at 0.2 ug/kg/hr and can be increased to 0.5-0.7 ug/kg/hr to maintain a mean arterial pressure of 55-65 mm Hg. Heart rate also decreases.³⁷

In many of these cases a direct acting vasodilator such as sodium nitroprusside, incardipine and fenoldopam is used for controlled hypotension. Disadvantages of any of these agents include reflex tachycardia, stimulation of the sympathetic nervous system especially with sodium nitroprusside with potential for rebound hypertension, also interference with hypoxic pulmonary vasoconstriction (HPV) and cerebral vasodilation with the potential of increased intracranial pressure (ICP) is possible. The decrease in HPV is particularly important in patients undergoing anterior spinal fusion needing one lung ventilation. Also the induced bradycardia with dexmedetomidine avoids the need for beta blocker use.

Sedation for Invasive Procedures

In a case report in an 11 year old for endoscopic gastrodeuodenoscopy, dexmedetomidine was administered in a bolus of 0.6 ug/kg followed by an infusion of 0.5 ug/kg/hr. Although being sleepy and unresponsive to verbal commands, with the introduction of the endoscope the patient became responsive and distressed. A significant level of sedation was not achieved, the infusion was discontinued and alternative sedation (midazolam and ketamine) was administered to complete the procedure.³⁷ Larger clinical trials are needed in children for use in these procedures.

Emergence Agitation

A single dose of IV dexmedetomidine 0.3 ug/kg after induction and maintenance of anesthesia with sevoflurane anesthesia decreased emergence agitation with no adverse effects.³⁹ In addition, a 1 ug/kg dose of IV dexmedetomidine reduces emergence agitation after sevoflurane anesthesia in children undergoing MRI.⁴⁰

Shivering

A single dose of dexmedetomidine 0.5 ug/kg over 3-5 min in 24 children aged 7-16 years with shivering caused cessation of the shivering in 5 minutes and no shivering recurred.⁴¹

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