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Recent Literature on the Use of Clonidine in Children and Adolescents

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Clonidine was approved as an antihypertensive medication by the Food and Drug Administration (FDA) in 1974, but it soon became adopted for other uses, including management of attention deficit/hyperactivity disorder (ADHD). It wasn't until the review of a new extended release formulation (Kapvay®) in October 2010 that the FDA approved clonidine for the treatment of ADHD as monotherapy or as adjunctive to stimulant medication.[1-3] In addition to this use, clonidine has played a role in a wide variety of conditions, including sleep disturbances, headaches, agitation following traumatic brain injury, and postoperative nausea and vomiting. This issue will review a selection of papers published in the last three years that suggest a growing role for clonidine in pediatric patients.

ADHD

The α_2-adrenergic agonists, clonidine and guanfacine, have been shown to improve symptoms of ADHD when used as monotherapy or in conjunction with stimulants or non-stimulant medications such as atomoxetine. They may be particularly useful as part of combination therapy in children with comorbidities such as Tourette syndrome or tic disorders.[4] The mechanism of action for these agents in ADHD may include both direct activity on presynaptic receptors in the prefrontal cortex and indirect modulation of input from the locus coeruleus to the prefrontal cortex via postsynaptic α_2A-adrenergic receptors. Sallee and colleagues provide an in-depth discussion of these potential mechanisms of action in their systematic review of the α_2-adrenergic agonists published in the June 2013 issue of the *Journal of Child and Adolescent Psychopharmacology*.[3] In addition, the authors provide a review of recent clinical trials involving these drugs as well as an overview of their pharmacokinetic properties and adverse effect profiles.

The efficacy and generally mild adverse effect profile of the α_2-adrenergic agonists has led to a steady rise in their use over the past decade. In a paper published last year in *Clinical Pediatrics*, Yoon and colleagues evaluated the increase in clonidine prescribing by assessing Michigan Medicaid claims.[1] The authors found that the proportion of children receiving clonidine nearly doubled over the period from 2003 to 2008. The greatest increase was in children treated for complex ADHD (ADHD with one or more comorbidities), while the use in simple ADHD remained constant. In their analysis, boys were more likely to receive clonidine than girls, and younger children (6-11 years of age) were more likely to be treated with it than adolescents. The growth of clonidine as part of a multidrug therapeutic approach was substantial. In data from 2008, 95% of children with simple ADHD and 89% of children with complex ADHD were receiving clonidine in addition to another agent.

One of the primary drawbacks of using clonidine for ADHD has been its relatively short half-life and the need for three or four doses per day. The introduction of Kapvay® in 2010 provided an extended release formulation that could be dosed once or twice daily. A second clonidine extended release tablet, Clonicel® (Sciele Pharma and Addrenex), is currently being studied in the United States (US).[5] Both products are initiated at a 0.1 mg dose at bedtime, with weekly titration based on response. As the total daily dose is increased, it may be split into morning and evening doses. In 2011, Kollins and colleagues published the results of a phase 3 randomized double-blind placebo-controlled trial in 198 children (6-17 years of age) with ADHD at 22 centers throughout the United States (US). All of the subjects were already receiving a stimulant. After 5 weeks, children in the clonidine group had significantly greater improvement from baseline in ADHD Rating

Scale IV scores (-15.7 compared to -11.5 for the placebo group, p = 0.009), hyperactivity subscale scores (-7.8 versus -5.8, p = 0.017), inattention subscale scores (-7.9 versus -5.8, p = 0.014), Conners' Parent Rating Scale scores (-40.2 versus -27.1, p = 0.017), Clinical Global Impression of Severity scores (-1.5 versus -1.2, p = 0.021), Clinical Global Impression of Improvement scores (-2.5 versus 3, p = 0.006), and Parent Global Assessment scores (2.7 versus 3.4, p = 0.001). The most frequently observed adverse effects were somnolence, headache, fatigue, and upper abdominal pain. The results of this study were similar to those from studies of Kapvay® and extended release guanfacine (Intuniv®) and support the efficacy of α_2-adrenergic agonists as adjuncts in the treatment of ADHD.

Insomnia/Early Awakening

Clonidine has been used off-label for many years as a short-term sedative for children with insomnia who fail to respond to non-pharmacologic methods or nonprescription therapies such as melatonin or first-generation antihistamines.[6] It has also been used as long-term therapy in children with neurologic impairment who have difficulty with sleep initiation or maintenance. In a 2013 survey of Australian pediatricians, 47% had prescribed clonidine for difficulties with sleep initiation failing to respond to melatonin and non-pharmacologic techniques.

Nguyen and colleagues at the University of Florida recently published an extensive review of clonidine as a sedative in children and adolescents.[7] The authors included information from a 2003 study of sedative use in six US community-based pediatric practices in which α_2-adrenergic agonists were the most commonly prescribed sleep aid.[8] The review also included the results of several retrospective studies and small clinical trials conducted in children with ADHD, autism spectrum disorders, and developmental delay. The authors conclude that clonidine has been shown to be beneficial in the papers published to date and is generally well tolerated, although they propose that additional research is needed to establish the efficacy and safety of long-term use in children.

Paroxysmal Autonomic Instability with Dystonia

Clonidine has become a standard part of the management of pain, anxiety, and paroxysmal autonomic instability with dystonia (PAID) in children and adolescents with acquired brain injury.[9-11] The symptoms of PAID, intermittent agitation, fever, hypertension, sinus tachycardia, dystonic movements, and diaphoresis, are often difficult to control and frequently require a combination of drugs. Traditional therapy has consisted of morphine, a beta-adrenergic blocking agent (propranolol, metoprolol, or labetalol), a benzodiazepine and/or baclofen to reduce muscle tone. The addition of clonidine or dexmedetomidine provides additional benefit in controlling both cardiovascular and CNS symptoms.

While PAID is most often associated with traumatic brain injury, it may occur after stroke, anoxic injury, or infection. Safadieh and colleagues recently described the management of PAID in a 7-month-old with *Streptococcus pneumoniae* meningitis who subsequently was found to have basal ganglia and hypothalamic infarctions.[12] Within weeks of diagnosis, the patient began to experience daily periods of agitation, hypertension, tachycardia, tachypnea, hyperthermia, and diaphoresis suggesting the development of PAID. Lorazepam and baclofen were started, as well as clonidine (3 mcg/kg given twice daily). The dose was slowly titrated to a final dose of 5 mcg/kg given four times daily. Symptoms were controlled until 8 weeks after admission when the patient developed hydrocephalus. The patient improved after receiving a ventriculoperitoneal shunt and clonidine was later successfully weaned off.

Therapeutic Hypothermia

Clonidine is used by many centers to prevent shivering in patients undergoing therapeutic hypothermia.[13] It has recently been suggested that it may be of additional benefit in neonates by providing neuroprotection after hypoxic ischemic injury. A phase 1,2 open-label clinical trial is currently being conducted at Johns Hopkins to evaluate the safety of clonidine in this population by assessment of the maximum tolerated dose, as well as its efficacy in preventing or stopping shivering.[14] Clonidine (Duraclon®) will be started at a dose of 1 mcg/kg given IV at dosing intervals of 4, 6, 8, or 12 hours. Dose escalation will stop if the patient develops hypotension or bradycardia. While it is anticipated that the study will take several years to be completed, the information obtained may support more widespread use of clonidine in this setting.

Cyclic Vomiting and Refractory Migraines

Several case reports describe the successful use of clonidine and dexmedetomidine in the management of cyclic vomiting associated with abdominal migraines.[15,16] A recent case report described a 6-year-old boy with cyclic vomiting who had failed therapy with analgesics, cyproheptadine, and sumatriptan.[17] He was

admitted after prolonged vomiting had produced dehydration, with resulting tachycardia and hypertension. He was treated with clonidine (1 mcg/kg given IV) with resolution of his hypertension as well as his vomiting for approximately 6 hours. At that time, he was given a 2 mcg/kg clonidine dose, which also resulted in symptom resolution and subsequent discharge. Two later episodes requiring hospitalization were also treated successfully with clonidine, along with ondansetron and a proton pump inhibitor. At that time, amitriptyline was initiated as prophylactic therapy, which reduced the frequency of subsequent admissions and the need for further clonidine. The authors suggest that a trial of clonidine be considered in children with cyclic vomiting who don't respond to conventional therapies.

Clonidine has a long history in the management of migraines in children and adolescents, but there is little evidence in the medical literature to support its use. Both a recent meta-analysis from the Medical College of Wisconsin and a systematic review conducted for the Agency for Healthcare Research and Quality found clonidine to be no more effective than placebo.[18,19] While not recommended as a first-line therapy for pediatric headaches, there may be individual patients with refractory migraines who benefit from clonidine as an adjunctive therapy.

Postoperative Nausea, Vomiting, and Agitation

Clonidine has also been used to reduce postoperative nausea and vomiting in children, although the results of previous clinical trials have been mixed.[20] Two recent randomized double-blind placebo-controlled studies have shown a benefit from premedication with oral clonidine. In a study of 60 children (ages 5-12 years) undergoing appendectomies, Alizadeh and colleagues found that those given a single 4 mcg/kg clonidine dose prior to surgery had significantly less nausea and emesis than those given a placebo.[21] Seventy-seven percent of patients experienced no nausea or emesis, compared to only 23% of the patients receiving placebo ($p < 0.001$).

In a study of 50 children undergoing strabismus surgery, Heinmiller and colleagues reported that those given a single dose of clonidine immediately after induction had significantly lower agitation scores during recovery.[22] In addition, more parents in the clonidine group rated themselves as very satisfied with their child's recovery (71% versus 46% of those whose children were given placebo), but the results were not significantly different.

Unintentional Exposures

Unfortunately, the rise in pediatric clonidine use has been accompanied by an increase in the number of unintentional exposures. In an article to be published in *The Journal of Pediatrics*, Wang and colleagues reviewed exposures to α_2-adrenergic agonists (clonidine, guanfacine, and tizanidine) in children 12 years of age and older that had been reported to the National Poison Data System (NPDS) between January 2000 and December 2011.[23] There were 27,825 clonidine, 6,143 guanfacine, and 856 tizanidine exposures, with a significant increase in cases reported over time (a 5.9% increase per year). For all three drugs, the patients were predominantly male, with a median age of 2 to 6 years. Clonidine exposure resulted in central nervous symptoms in 45.3% of patients, bradycardia in 10.2%, hypotension in 8.5%, and respiratory compromise in 2.9%. There were seven cardiac arrests and three deaths, all associated with clonidine. The deaths included accidental ingestions with aspiration and a compounding error resulting in an overdose. These cases underscore the need for educating families about safe medication storage and highlight the risks of compounding liquid preparations.

The management of symptomatic clonidine exposures varies among treatment centers. While the use of atropine and administration of IV fluids to resolve cardiovascular and hemodynamic instability is routine, administration of naloxone to reverse the central nervous system effects of α_2-adrenergic agonists remains controversial. In the NPDS study, 26 children (11.8%) received naloxone.[23] The rationale for using naloxone in this setting is based on the potential for reversal of the vasodilation resulting from catecholamine suppression produced by endogenous opioids released during periods of acute stress.[23,24]

The utility of naloxone in the setting of clonidine overdose was reviewed in a recent paper by Ahmad and colleagues.[24] The authors describe a case of clonidine toxicity in a 2-year-old child who presented with hypotension, hypotonia, lethargy, and respiratory depression requiring intubation after ingestion of an unknown quantity of clonidine tablets. A trial dose of naloxone (0.1 mg/kg) was administered IV, but produced no change in clinical status. The patient responded to supportive therapy with 20 mL/kg boluses of normal saline and a 0.02 mg/kg dose of atropine. Based on this case and their review of the literature, the authors suggest that the use of naloxone does not appear to be justified in this setting.

Summary

Clonidine has found a niche in the management of a variety of neurologic conditions. With the advent of extended release products and new studies demonstrating its utility in a range of conditions from ADHD to neuroprotection during therapeutic cooling, clonidine is likely to remain an important therapeutic tool for use in children and adolescents.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their October meeting:

1. C1 Esterase inhibitor, human (Berinert®) was added to the Formulary for the treatment of acute swelling associated with hereditary angioedema.
2. A transdermal formulation of buprenorphine (Butrans®) was added for the management of severe pain, with restriction to the Chronic Pain Service and Palliative Care.
3. Several agents were approved for use by Ophthalmology. Ocriplasmin (Jetrea™) was added to the Formulary for the treatment of symptomatic vitreomacular adhesions. An intravitreal preparation of dexamethasone (Ozurdex®) was added for treatment of macular edema following branch or central retinal vein occlusion or treatment of noninfectious uveitis affecting the posterior segment of the eye. Methazolamide (Neptazane™) was added for patients requiring lowering of intraocular pressure prior to surgery.
4. The commercially prepared lansoprazole suspension product (First®-Lansoprazole) was added.

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