Pulmonary hypertension, whether primary or resulting from congenital cardiac disease, remains one of the most difficult childhood diseases to treat. Currently available vasodilators, such as inhaled nitric oxide and continuous intravenous infusions of epoprostenol (prostacyclin), are limited by expense and ease of use. Sildenafil, a vasodilator developed for the treatment of erectile dysfunction, has recently been used by several investigators as an alternative to traditional therapies to dilate the pulmonary vasculature. It offers the convenience of oral dosing, has relatively few adverse effects, and costs substantially less than other agents.

Mechanism of Action
Sildenafil is a selective inhibitor of phosphodiesterase type 5 (PDE5). Present throughout the body, PDE5 is found in high concentrations in the lungs. Inhibition of PDE5 enhances the vasodilatory effects of nitric oxide in pulmonary hypertension by preventing the degradation of cyclic guanosine monophosphate (cGMP), which promotes relaxation of vascular smooth muscle and increases blood flow. In animal models and human trials, sildenafil has been found to produce a relatively selective reduction in pulmonary artery pressure without adverse systemic hemodynamic effects. Inhibition of PDE5 by sildenafil may also enhance the platelet antiaggregatory activity of nitric oxide and inhibit thrombus formation.

Use in Pulmonary Hypertension
In 1999, Atz and Wessel described three cases in which oral sildenafil was used to lessen the effects of sudden discontinuation of inhaled nitric oxide. The three patients, newborn to 4 months of age, were receiving nitric oxide for pulmonary hypertension following surgical repair of congenital cardiac lesions. At the time of discontinuing nitric oxide, the patients were given a 1 to 1.1 mg dose of sildenafil via nasogastric tube. In two of the cases, circulating cGMP concentrations rose significantly after sildenafil administration. Both patients were weaned from nitric oxide without difficulty. The response was less dramatic in the third case, which was felt to be the result of impaired drug absorption. Based on their initial results, the authors concluded that sildenafil was effective in increasing intracellular and circulating stores of cGMP, and may be beneficial in preventing the rapid depletion of cGMP and rebound hypertension seen when discontinuing inhaled nitric oxide therapy.

The following year, Abrams, Schulze-Neick, and Magee reported the use of chronic sildenafil therapy in a 4 year old child with primary pulmonary hypertension. Oral sildenafil was instituted at a dose of 2 mg/kg every 6 hours following a poor response to intravenous prostacyclin. Serial measurement of oxygen saturation showed a 10% rise that lasted 60 to 90 minutes following each dose. As a result, the dosing frequency was increased to every 4 hours with continued improvement in clinical status. Both prostacyclin and supplemental oxygen were discontinued. Follow-up three months later showed continued improvement in exercise tolerance and no adverse effects.

In 2002, Atz and coworkers published another case report describing use of sildenafil in combination with inhaled nitric oxide in a 9 month old child with repeated pulmonary hypertensive crises following mitral valve replacement. Sildenafil was administered at an initial dose of 0.3 mg/kg through a nasogastric tube, with subsequent dosing every 4 hours. The administration of sildenafil allowed the gradual...
weaning of nitric oxide, with discontinuation on postoperative day 15. Mean pulmonary artery pressure remained approximately 60 to 70% of mean systemic blood pressure throughout treatment. Sildenafil was discontinued on postoperative day 22 without rebound pulmonary hypertension or adverse effects.

In the July-August 2002 issue of the Indian Heart Journal, Kothari and Duggal published an additional series of 14 patients ranging from 5 to 30 years of age who were given oral sildenafil as chronic therapy for pulmonary hypertension. Nine patients had primary pulmonary hypertension, and the remaining five had pulmonary hypertension after repair of congenital cardiac defects. All were receiving standard therapies when sildenafil was initiated. The median dose used was 87.5 mg/day in children under 30 kg and 150 mg/day in larger patients. At follow-up (mean 7.3±2.4 months), there were statistically significant improvements in New York Heart Association functional class and 6-minute walk testing. Right ventricular systolic pressure declined from 112.40±45.21 to 101.86±47.86 mm Hg. Clinical improvement was reported in all patients, even those with marginal changes in pulmonary artery pressure.

Carroll and Dhillon reported three more pediatric cases last year. Two of their patients, ages 1 and 2 years, had primary pulmonary hypertension, and one newborn had postoperative pulmonary hypertension following repair of transposition of the great arteries. The patients were started on sildenafil at doses ranging from 0.5 to 1 mg/kg every 6 hours and titrated up to a final dose of 2 mg/kg every 6 hours. Two of the patients showed an initial positive response, while one patient remained unchanged. None of the children experienced adverse effects. As in the earlier cases, the authors suggested that sildenafil be considered an alternative option for children with pulmonary hypertension who require long-term therapy.

In addition to these case reports, Erickson and colleagues from Toronto’s Hospital for Sick Children recently published an abstract describing oral sildenafil in 16 children with pulmonary hypertension. The patients ranged in age from 3 days to 18 years, with a median age of 6 years. Sildenafil doses ranged from 0.25 to 0.5 mg/kg. Eleven patients were treated short-term, following nitric oxide administration. In six patients, hemodynamic response to sildenafil was evaluated during cardiac catheterization. Mean pulmonary artery pressure decreased from 50±8 to 38±12 mm Hg. Pulmonary vascular resistance decreased from 10.5±4.9 to 7.6±4.6 Wood Units*m⁻². Mean systemic pressure, systemic vascular resistance, and cardiac index remained unchanged. In addition, the authors reported sustained improvement in three of the five patients who received long-term therapy with sildenafil given four times daily.

Last year, Schulze-Neick and colleagues conducted another study of sildenafil during cardiac catheterization in 24 children. Twelve of the patients studied (ages 0.2 to 15.7 years) had increased mean pulmonary arterial pressures associated with unrepaired congenital heart disease. Another 12 children were studied immediately after returning from cardiac surgery (ages 1 to 7 months). The effects of inhaled nitric oxide were compared to a stepwise infusion of intravenous sildenafil (up to approximately 1 mg/kg during catheterization or 0.25 mg/kg postoperatively). The authors found that sildenafil produced a greater reduction in pulmonary vascular resistance than nitric oxide and potentiated the increase in cGMP produced by nitric oxide. Although sildenafil was well tolerated overall, an increased intrapulmonary shunting was observed, which the authors cautioned may be a disadvantage to its use in the immediate postoperative period.

A number of papers have also been published describing the efficacy of sildenafil in adults with pulmonary hypertension. In a recent paper by Ghofrani and colleagues, 14 adults with severe pulmonary hypertension refractory to conventional therapies were given oral sildenafil (25 to 50 mg three times daily) in conjunction with inhaled iloprost, a prostacyclin analog, for a period of 9 to 12 months. At baseline, mean 6 minute walking distance was 217±31 m. Treatment improved the distance to 346±26 m. Benefit was sustained for up to 12 months. Hemodynamic variables and New York Heart Association functional class also improved.

Pharmacokinetics
The pharmacokinetic profile of sildenafil has not been evaluated in children. In adults, it is rapidly absorbed after oral administration, with a bioavailability of approximately 40%. Maximum serum concentrations occur 0.5 to 2 hours after an oral dose. Administration with a high-fat meal slows absorption and reduces maximum plasma concentrations by 30%. Sildenafil is highly protein bound (96%) and extensively distributed throughout the body. It is metabolized via the hepatic cytochrome P450 (CYP) enzyme system, primarily by CYP3A4 and to a lesser degree by CYP2C9. In addition, an active metabolite is formed through N-desmethylation. The elimination half-life of
sildenafil is approximately 4 hours in adults. Clearance is reduced in patients with moderate to severe renal or hepatic function.  

**Drug Interactions**
Because of their ability to inhibit CYP3A4 enzyme activity, sildenafil should not be administered withazole antifungals, clarithromycin, erythromycin, and protease inhibitors such as indinavir, ritonavir, and saquinavir. Administration with the nonspecific enzyme inhibitor cimetidine increases plasma sildenafil concentrations by approximately 50%. Rifampin, an inducer of CYP3A4, decreases levels of sildenafil. Concomitant administration with other antihypertensive agents, including nitrates, alpha blocking agents, and calcium channel blockers such as amlodipine and nifedipine, may result in excessive hypotension.  

**Adverse Effects**
The most frequently reported adverse effects with sildenafil include headache (16% of adults in clinical trials), flushing (10%), stomach upset (7%), nasal congestion (4%), diarrhea or urinary tract infection (3%), and rash or dizziness (2%). A minor reduction in blood pressure has also been reported in clinical trials. Abnormal vision has been reported in up to 11% of patients, typically a mild and transient change in color discrimination. Increased sensitivity to light and blurred vision have also been reported. This effect appears to be more common in patients receiving higher doses (eg, 100 mg) and is likely the result of inhibition of PDE6 in the retina. Sildenafil has not been associated with changes in intraocular pressure. 

Other rare adverse effects reported with sildenafil in adults (all < 2%) include: arrhythmias, cerebral thrombosis, hypertonia, paresthesias, priapism, migraine, tremor, photosensitivity, colitis, vomiting, abnormal liver function tests, anemia, leukopenia, gout, arthritis, dyspnea, and allergic reactions.  

**Dosing Recommendations**
Based on the case reports and studies conducted with sildenafil to date, an initial dose of 0.25 to 0.5 mg/kg given orally every 4 to 8 hours is recommended for pediatric patients with pulmonary hypertension. Dose titration should be based on response. Although no maximum dose has been determined, doses above 2 mg/kg every 4 hours may not provide additional benefit. In adults with pulmonary hypertension, sildenafil is typically initiated at a dose of 25 mg every 6 to 8 hours. Doses up to 100 mg five times daily have been reported in adults with severe disease.  

**Availability and Cost**
Sildenafil (Viagra®; Pfizer) is available in 25, 50, and 100 mg tablets. The average wholesale price for a bottle of 30 tablets (25 mg) is $287.68. An extemporaneous preparation for an oral liquid was recently presented at the American Society of Health-System Pharmacists meeting. Nahata and colleagues reported that sildenafil suspensions (2.5 mg/ml) made with either a 1% methylcellulose and simple syrup (1:1) mixture or a 1:1 mixture of OraSweet® and OraPlus® were stable for one month at room temperature or under refrigeration.  

**Summary**
Sildenafil appears to be a useful alternative to traditional therapies for pulmonary hypertension. The availability of an oral dosage form and its relatively mild adverse effect profile make it an appealing option for children requiring long-term therapy. More research is needed, however, to develop an optimal regimen for dose titration and establish long-term efficacy.  

**References**
Pharmacology Literature Review

Atomoxetine in Adults

With an increasing number of patients being diagnosed, the treatment of attention deficit/hyperactivity disorder (ADHD) in adults has received considerable attention over the past year. This review focuses on two 10-week adult trials of atomoxetine, the first nonstimulant medication developed for ADHD. The authors also provide a review of the adverse effect profile and dosing of atomoxetine in ADHD. Simpson D, Plosker GL. Atomoxetine: a review of its use in adults with attention deficit hyperactivity disorder. Drugs 2004;64:205-22.

Epoetin dosing in children

The authors of this study suggest that weight-based dosing of epoetin in children with renal disease is unnecessary and can lead to excessive doses. The response to epoetin was studied in 52 patients between 5 and 20 years of age. Epoetin was administered three times weekly after hemodialysis (dose range 3 to 205 IU/kg). Using both nonlinear mixed-effects modeling and nonparametric analysis, the authors found that dose-response was best described by a sigmoid maximum-effect model. Dose-response outcomes did not show dependence on weight. Median hemoglobin levels after use of a standard dose in children were similar to those seen after routine dosing in adults, supporting the authors contention that weight-based dosing is not needed to optimize epoetin response. Port RE, Kiepe D, Van Guilder M, et al. Recombinant human erythropoietin for the treatment of renal anaemia in children: no justification for bodyweight-adjusted dosage. Clin Pharmacokinet 2004;43:57-70.

Omeprazole pharmacokinetics

In order to compare pediatric and adult pharmacokinetic parameters for omeprazole, the authors of this study evaluated 18 adults and 12 children with gastroesophageal reflux. Adults received a 20 mg oral dose, while the children were given either a 10 or 20 mg dose once daily for a period of 8 weeks. Using standard population pharmacokinetic modeling techniques, the authors found a clearance and apparent volume of distribution in children that were similar to that seen in adults (0.51±0.34 L/hr/kg and 0.66±0.25 L/kg versus 0.62±0.27 L/hr/kg and 0.76±0.26 L/kg, respectively). Values for elimination half-life were also similar (1.07±0.42 hr for children versus 0.90±0.17 hr for adults). The only difference identified was a longer drug absorption phase in adults. Based on their findings, the authors suggest that the pharmacokinetic profile of omeprazole in children is similar to that observed in adults. Marier J, Dubuc M, Drouin E, et al. Pharmacokinetics of omeprazole in healthy adults and in children with gastroesophageal reflux disease. Ther Drug Monit 2004;26:3-8.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 1/23/04:

1. Fosamprenavir (Lexiva®), a pro-drug of the HIV protease inhibitor amprenavir, was added to both the Inpatient and Outpatient Formularies for the treatment of HIV infection.
2. A combination otic product with 0.3% ciprofloxacin and 0.1% dexamethasone (Ciprodex®) was also added to the Inpatient and Outpatient Formularies. Use is restricted to Otolaryngology-Head and Neck Surgery.
3. Amoxicillin/clavulanate potassium extended-release tablets (Augmentin XR®) and powder for oral suspension (Augmentin ES™) were added to the Outpatient Formulary.

Contributing Editor: Marcia L. Buck, Pharm.D.
Editorial Board: Anne E. Hendrick, Pharm.D. Michelle W. McCarthy, Pharm.D. Kristi N. Hofer, Pharm.D.

If you have comments or suggestions for future issues, please contact us at Box 800674, UVA Health System, Charlottesville, VA 22908 or by e-mail to mhb3u@virginia.edu. This newsletter is also available at www.healthsystem.virginia.edu/internet/pediatrics/pharma-news/home.cfm