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Use of Carvedilol in Children with Cardiac Failure

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Beta-adrenergic blocking agents have become important tools in the management of heart failure. Over the past two decades, a number of clinical trials have shown the beneficial effects of these agents in reducing the myocyte injury and hemodynamic deterioration associated with chronic adrenergic overstimulation.[1] Carvedilol, approved by the Food and Drug Administration in 1995, was the first agent of the class to receive an indication for the treatment of heart failure.[1-3] While currently approved only for use in adults, several reports have documented the efficacy of carvedilol in improving the functional status of children with heart failure.[4-12] This issue of *Pediatric Pharmacotherapy* will review the use of carvedilol in children, as well as provide information on dosing and monitoring.

Mechanism of Action

Carvedilol is a racemic mixture with nonselective beta-adrenergic blocking activity produced by the S(-) enantiomer and alpha$_{(1)}$-adrenergic blocking activity provided by both the R(+) and S(-) enantiomers in equal potency. It has no intrinsic sympathomimetic activity.[2,3]

Beta-adrenergic blocking agents are believed to improve cardiac failure by reducing circulating catecholamine concentrations. High levels of catecholamines, while useful in the short-term to increase cardiac output, result over time in increased cellular necrosis, increased myocardial oxygen consumption, ventricular hypertrophy, and fibrosis. By reducing catecholamines, beta-adrenergic blocking agents improve systolic function, decrease fibrotic remodeling of dilated ventricles, improve clinical symptoms, and have been associated with decreased hospitalization and mortality.[1]

It has been suggested that these agents also reduce QT dispersion, reducing the potential for sudden death from arrhythmia. Although documented in adults, this effect has not been demonstrated in children.[13] Carvedilol provides the additional benefits of systemic arterial vasodilation through its alpha-blocking activity, anti-oxidant, and anti-endothelin effects.[2,3]

Use in Children with Cardiac Failure

In 2001, the first two articles documenting the use of carvedilol in children were published.[4,5] Bruns and colleagues reported the experiences of 6 centers who had treated a total of 46 children between 3 months and 19 years of age.[4] Thirty-seven of the patients had a dilated cardiomyopathy, while nine had congenital heart disease. Therapy was initiated at a dose of 0.08 mg/kg given twice daily, and titrated as needed to an average dose of 0.46 mg/kg (0.92 mg/kg/day). After three months of therapy, 67% of the patients had an improvement in their modified New York Heart Association (NYHA) class. Mean shortening fraction improved from 16.2% to 19%. While the majority of the patients improved or remained stable, 30% were considered to have adverse outcomes (death or the need for transplantation or a ventricular-assist device) despite treatment. The authors concluded that carvedilol was a useful adjunct to standard therapy for pediatric cardiac failure.

Gachara and colleagues published their experience with carvedilol in eight infants with dilated cardiomyopathy.[5] All patients were receiving digoxin, diuretics, and captopril. The average age at the start of therapy was 11$\pm$6.8 months. An initial dose of 0.1 mg/kg was given twice daily. The dose was titrated every 24 hours as needed, with an average maintenance dose of 1.08$\pm$0.4 mg/kg/day. At follow-up (4.5$\pm$2.2 months), the patients showed significant improvement over baseline, with an increase in left ventricular ejection fraction (LVEF) from 24.4$\pm$5% to 38.5$\pm$11%. Five of the patients became asymptomatic, and two had only mild symptoms.

In 2002, Laer and colleagues reported the results of an open-label trial of carvedilol in 15 patients (6 weeks to 19 years of age) with cardiac failure who failed traditional management.[6] Ten had dilated cardiomyopathy, and five had congenital

heart disease. Carvedilol was started at 0.09 mg/kg twice daily and titrated at 2-week intervals to a maximum of adult dose of 50 mg/day. The target maintenance dose was 0.7 mg/kg/day. Twelve patients completed the 6-month trial, with a significant improvement in LVEF from 36% to 54%. Clinical symptom scores also showed statistically significant improvement. Mean arterial pressure declined from 75 mm Hg to 60 mm Hg and heart rate decreased from 116 beats/min to 96 beats/min.

Williams and colleagues from the University of Utah conducted a retrospective review of their experience with carvedilol and metoprolol in 12 children with left ventricular systolic dysfunction.[8] All patients had remained symptomatic on traditional therapy. Six patients were given metoprolol (0.4-2.4 mg/kg/day) and six received carvedilol (0.4-0.9 mg/kg/day). At six months, there was a significant increase in both shortening fraction (from 13±4% to 21±8%) and LVEF (from 26±8% to 41±17%). There were no significant differences between the patients given metoprolol and those given carvedilol. An early response to beta-adrenergic blocker therapy was associated with increased survival and reduced need for transplantation.

Azeka and colleagues conducted a prospective, randomized, double-blind, placebo-controlled trial of carvedilol in 22 children with refractory heart failure.[9] Carvedilol was initiated with a low dose of 0.01 mg/kg/day and increased as needed up to a target dose of 0.2 mg/kg/day. At six months, there was a significant increase in LVEF in the carvedilol group (from 17.8% at baseline to 34.6%). Modified NYHA class improved in 9 of the 14 patients, allowing them to be removed from the transplant waiting list. Patients in the placebo group showed no improvement; two died and two required transplantation.

In 2003, Giardini and colleagues studied the effects of carvedilol in nine children with dilated cardiomyopathy over a one-year period.[10] Therapy was initiated at 0.05 mg/kg/day and increased every 1-2 weeks to a target dose of 0.8 mg/kg/day. At 12-month follow-up, plasma concentrations of norephinephrine, dopamine, and aldosterone were significantly reduced compared to baseline. Positive effects on ventricular remodeling were noted, with significant reductions in end-diastolic and end-systolic diameters, and an increase in LVEF.

Maunoury and colleagues demonstrated a similar benefit in 17 children (average age 39±57 months) given carvedilol.[11] Treatment was initiated with a dose of 0.01 mg/kg/day and titrated to 0.2 mg/kg/day. After 6 months, LVEF increased from 26±11% to 43±17%, with 13 of the patients exhibiting more than a 10% improvement. In addition, the study showed a 38% increase in cardiac uptake of iodine-123 metaiodobenzylguanidine, representing a significant improvement in cardiac adrenergic neuronal function.

An additional retrospective review of carvedilol in children was reported in the *Journal of Heart and Lung Transplantation* last year.[12] Rusconi and colleagues from the University of Miami reported their experience over a 3-year period. Carvedilol was added to standard therapy in patients with a persistent LVEF ≤ 40%. The review included 24 children between 1 day and 16.5 years of age. The average initial and final doses were 0.15±0.09 mg/kg/day and 0.98±0.26 mg/kg/day, respectively. Two patients discontinued therapy, one for asthma and the other for worsening cardiac failure. In the remaining patients, there was a significant increase in LVEF from 24.6±7.6% to 42.2±14.2%. Fifteen patients (68%) had improvement in their NYHA functional class. One patient died and 3 received transplants.

In addition to these reports, a multicenter trial of carvedilol in children with heart failure is currently underway. With an expected enrollment of 150 children, this placebo-controlled study has been designed to address a composite of clinical outcomes including mortality, hospitalization, and symptomatic improvement, as well as measuring indices of ventricular function.[14]

Pharmacokinetics

After oral administration, carvedilol is well absorbed. The bioavailability is approximately 25 to 35%, because of significant first-pass metabolism. Administration with food slows the rate of carvedilol absorption, but does not affect bioavailability. Carvedilol is widely distributed and more than 98% protein bound.

Carvedilol is extensively metabolized through aromatic ring oxidation and glucuronidation. The primary cytochrome P450 enzymes involved include CYP2D6 and CYP2C9, and to a lesser extent, CYP3A4, 2C19, 1A2, and 2E1. Three active metabolites are produced, with significant beta-adrenergic blocking activity, but only weak vasodilating activity. The oxidative metabolites are then further metabolized by conjugation through glucuronidation and sulfation and excreted in bile. In adults, the mean elimination

half-life is 5 to 9 hours for R(+)-carvedilol and 7 to 11 hours for S(-)-carvedilol.

During their open-label trial, Laer and colleagues compared the pharmacokinetic profile of carvedilol in the 15 children enrolled with nine healthy adults.[6] In their study, the children exhibited higher maximum serum concentrations (average 16.9 ng/ml in children versus 11.2 ng/ml in adults), although AUC values were similar. Elimination half-life was significantly shorter in the pediatric patients than in the adults (2.9 versus 5.2 hours). When the pediatric patients were further divided into two groups (those <3.5 years and those older), the average elimination half-life was 2.2 hours in the younger children versus 3.6 hours in the older patients.

Adverse Effects

As with other beta-adrenergic blocking agents, carvedilol is not recommended for patients with asthma or bronchospastic disease, diabetes, hepatic dysfunction, hyperthyroidism, or significant peripheral vascular disease.

The most commonly reported adverse effects with carvedilol include postural hypotension or bradycardia (2-10% of adults in clinical trials), angina or syncope (2-8%), dizziness (6-32%), headache (5-8%), edema (1-5%), insomnia (2%), diarrhea (2-12%), nausea or vomiting (1-9%), respiratory, urinary tract or viral infections (1-18%), arthralgias, asthenia or fatigue (1-24%), cough or rales (4-8%), hyperglycemia (5-12%), elevated triglyceride levels or hypercholesterolemia (1-4%), and thrombocytopenia (1%).

In addition, there have been rare reports of changes in vision, severe hypersensitivity reactions, and renal function impairment associated with carvedilol use. Hepatoxicity has been observed in clinical trials of adults (1.1% versus 0.9% of controls). Hepatic injury has been reversible upon discontinuing carvedilol.

In pediatric studies, adverse effects have been common but mild. Bruns reported dizziness (in 19% of patients), hypotension (14%), headache (14%), vomiting (9%), fatigue or dyspnea (7%), edema (5%), chest pain, reflux, atrial flutter, and syncope (in 2% each).[4] Rusconi reported an exacerbation of reactive airway disease, dizziness, or hypotension (each in 8% of patients), worsening cardiac failure, bradycardia, emesis, headache, and arrhythmia (each in 4%). Thirteen of the 22 patients who completed the study remained on therapy for more than 2 years with minimal adverse effects.[12]

Drug Interactions

Carvedilol interacts with a number of other drugs as a result of its metabolism through cytochrome P450 enzymes. When administered with rifampin, the area under the curve (AUC) and maximum concentration of carvedilol are decreased by approximately 70%. Administration with cimetidine increases the AUC of carvedilol by 30%, but does not alter the maximum concentration.

Concomitant use of carvedilol and digoxin has been shown to increase digoxin AUC by 14% in adults. In 2003, Ratnapalan and colleagues studied the interaction in eight children.[15] Digoxin clearance declined from 153.0$\pm$92.3 ml/min/1.73m^2 to 80.6$\pm$23.9 ml/min/1.73m^2 after four days of concomitant carvedilol administration. All patients had an increase in serum digoxin concentrations, with two patients having levels above the therapeutic range. Based on their observations, the authors recommend reducing the dose of digoxin by 25% in children receiving carvedilol.

Administration of carvedilol with cyclosporine may also increase cyclosporine serum concentrations. Both digoxin and cyclosporine concentrations should be closely monitored when initiating or titrating carvedilol, with dosage adjustment as needed.

Although not well studied, there is a potential for reduced carvedilol clearance in patients receiving concurrent therapy with selective serotonin reuptake inhibitors, diphenhydramine, hydroxychloroquine, propafenone, or quinidine. Carvedilol may also reduce the clearance of disopyramide. It may also increase the pharmacologic response to insulin or oral hypoglycemics, calcium channel blocking agents, or clonidine because of its beta-adrenergic blocking properties. Patients receiving catecholamine-depleting agents such as reserpine or monoamine oxidase inhibitors should be closely monitored when initiating carvedilol because of the risk for severe hypotension or bradycardia.

Dosing and Administration

Based on the studies performed to date, carvedilol should be initiated in infants and children at a dose of 0.05 to 0.2 mg/kg/day, divided and given twice daily. The dose may be titrated at 1 to 2 week intervals as needed. In most of the papers cited, the average effective dose was 0.2 to 1 mg/kg/day, with a suggested maximum of 2 mg/kg/day.

Families should be instructed not to discontinue carvedilol abruptly. Children receiving carvedilol should be watched for dizziness when standing, especially during the first weeks of therapy or following an increase in dose. Carvedilol may cause photosensitivity, so patients should use sunscreen and wear protective clothing when outdoors.

Availability

Carvedilol is available as Coreg® (GlaxoSmithKline) in 3.125, 6.25, 12.5, and 25 mg tablets. While there is no commercially available oral liquid formulation of carvedilol, an extemporaneous formulation can be prepared from the tablets. The manufacturer has studied two formulations, the first using one 3.125 mg tablet and the second using two 25 mg tablets. After crushing the tablets, the powder should be mixed with 5 ml water, 15 ml Ora-Plus®, and 10 ml Ora-Sweet®, to make a final volume of 30 ml. These preparations result in final concentrations of 0.1 mg/ml and 1.68 mg/ml, respectively. These formulations may be stored for up to 12 weeks at room temperature.[16]

Summary

Carvedilol, an agent with both alpha- and beta-adrenergic blocking properties, has been shown to provide significant benefit in adult patients with cardiac failure. Over the past four years, several studies have confirmed its efficacy in the pediatric patient population as well. Additional work, including more longitudinal studies, is needed to confirm the findings of these early reports.

References

1. Spicer RL. Carvedilol-a new dimension in pediatric heart failure therapy. [editorial] J Pediatr 2001;138:457-8.
2. Carvedilol. *Drug Facts and Comparisons*. Efacts [online]. 2004. Available from Wolters Kluwer Health, Inc. Accessed 1/6/05.
3. Coreg® prescribing information. GlaxoSmithKline, October 2003.
4. Bruns LA, Chrisant MK, Lamour JM, et al. Carvedilol as therapy in pediatric heart failure: an initial multicenter experience. J Pediatr 2001;138:505-11.
5. Gachara N, Prabhakaran S, Srinivas S, et al. Efficacy and safety of carvedilol in infants with dilated cardiomyopathy: a preliminary report. Indian Heart J 2001;53:74-8.
6. Laer S, Mir TS, Behn F, et al. Carvedilol therapy in pediatric patients with congestive heart failure: a study investigating clinical and pharmacokinetic parameters. Am Heart J 2002;143:916-22.
7. Horenstein MS, Ross RD, Singh TP, et al. Carvedilol reverses elevated pulmonary vascular resistance in a child with dilated cardiomyopathy. Pediatr Cardiol 2002;23:100-2.
8. Williams RV, Tani LY, Shaddy RE. Intermediate effects of treatment with metoprolol or carvedilol in children with left ventricular systolic dysfunction. J Heart Lung Transplant 2002;21:906-9.
9. Azeka E, Ramires JAF, Valler C, et al. Delisting of infants and children from the heart transplantation waiting list after carvedilol treatment. J Am Coll Cardiol 2002;40:2034-8.
10. Giardini A, Formigari R, Bronzetti G, et al. Modulation of neurohormonal activity after treatment of children in heart failure with carvedilol. Cardiol Young 2003;13:333-6.
11. Maunoury C, Acar P, Sidi D. Use of ^{123}I-MIBG scintigraphy to assess the impact of carvedilol on cardiac adrenergic neuronal function in childhood dilated cardiomyopathy. Eur J Nucl Med Mold Imaging 2003;30:1651-6.
12. Rusconi P, Gomez-Marin O, Rossique-Gonzalez M, et al. Carvedilol in children with cardiomyopathy: 3-year experience at a single institution. J Heart Lung Transplant 2004;23:832-38.
13. Etheridge SP, Shaddy RE. QT dispersion after beta-blocker therapy (carvedilol or metoprolol) in children with heart failure. Am J Cardiol 2003;91:1497-500.
14. Shaddy RE, Curtin EL, Sower B, et al. The pediatric randomized carvedilol trial in children with chronic heart failure: rationale and design. Am Heart J 2002;144:383-9.
15. Ratnapalan S, Griffiths K, Costei AM, et al. Digoxin-carvedilol interactions in children. J Pediatr 2003:142:572-4.
16. Personal communication, GlaxoSmithKline. 1/11/05.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/28/05:

1. Natalizumab (Tysabri®) was added to the Inpatient Formulary with restriction to Neurology for the treatment of patients with relapsing forms of multiple sclerosis.
2. Chlorothiazide (Diuril®) was added to the Outpatient Formulary with a restriction to Pediatrics.
3. The following drugs were removed from the Inpatient Formulary: ammonium chloride injection, sodium lactate injection, calcium carbonate tablets, calcium gluconate tablets, potassium bicarbonate effervescent tablets, amiloride, chlorthalidone, and triamterene.
4. The following drugs were removed from the Outpatient Formulary: calcium gluconate tablets, potassium bicarbonate effervescent tablets, amiloride, and chlorthalidone.
5. The quarterly results of the Adverse Drug Reaction (ADR) reporting program were presented. A total of 166 ADR reports were submitted, with 46% classified as moderate and 34% as severe. The most common agents involved were anti-infectives (20.5%), analgesics (15%), and antineoplastics (10%). For additional information about the report, please contact Drug Information Services at 4-8034.

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