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Aldosterone Inhibitors in Infants and Children

Marcia L. Buck, Pharm.D., FCCP

Spironolactone has been available in the United States since the 1950s; but over the past several decades, its use has been supplanted by newer agents, such as the angiotensin converting enzyme inhibitors and angiotensin receptor blocking agents. With the 1999 publication of the Randomized Aldactone Evaluation Study (RALES)[1] which showed a 30 percent reduction in risk of death when spironolactone was added to standard therapy for severe heart failure, there has been a renewed interest in aldosterone inhibitors. The subsequent development of eplerenone, a new agent with fewer adverse effects than spironolactone, has further increased the utility of aldosterone inhibitors in adults.[2]

In children, spironolactone has been used for more than 40 years to treat heart failure associated with congenital heart disease and to alleviate pulmonary congestion in neonates with chronic lung disease. Despite the frequency of its use in children, there have been very few studies to document the efficacy and safety of spironolactone in this population. In an effort to stimulate new research, the Food and Drug Administration placed spironolactone on its "List of Drugs for Which Pediatric Studies Are Needed" in 2003.[3] This issue of *Pediatric Pharmacotherapy* will review the available information on spironolactone in children and highlight potential areas for further research with the aldosterone inhibitors.

Mechanisms of Action

Spironolactone and eplerenone are competitive aldosterone receptor antagonists. Aldosterone is primarily secreted by the adrenal gland in response to intravascular volume depletion and/or excessive sodium loss. Higher concentrations are secreted during periods of physiologic stress. In the renal collecting duct and distal tubule, aldosterone increases absorption of sodium in exchange for potassium and hydrogen ions. By inhibiting aldosterone activity, spironolactone reduces sodium reabsorption, producing diuresis. It is considered a relatively weak diuretic, blocking less than 2% of the total filtered sodium load.[4]

While the diuretic effect of spironolactone has long been considered its primary mechanism of action, more recent studies have focused on its role in blocking aldosterone production in the vascular tissue of patients with heart failure. Local production of aldosterone may lead to myocardial and aortic remodeling, with fibrosis, and nephrosclerosis. In addition, the sustained elevations in aldosterone concentrations seen in patients with heart failure may cause abnormal vasomotor reactivity and baroreceptor responsiveness. Inhibition of aldosterone by either spironolactone or eplerenone appears to prevent these fibrotic changes and improves cardiac sympathetic nerve function in adults.[4-7] No studies have been published yet to confirm these benefits in children with heart failure.

Use of Spironolactone in Chronic Lung Disease

The first reported use of spironolactone in children was in a series of experiments with diuretics in newborns conducted by Walker and Cummings in 1964.[8] In this study, three infants were given 50 mg spironolactone in divided doses. The drug produced a modest increase in urine flow, from a baseline of 445 to 469 ml/24 hours after treatment. Sodium excretion increased from 24.1 to 27.2 mEq/24 hours, while potassium excretion was unchanged. In 1974, Sole and Knorr studied intravenous spironolactone in 9 newborns and 13 infants and reported similar findings of mild diuresis with decreased potassium excretion.[9]

Since these initial reports, several investigators have studied the effectiveness of spironolactone in the management of pulmonary edema in preterm neonates with bronchopulmonary

dysplasia/chronic lung disease (CLD), with mixed results. In 1984, Kao and colleagues published the first clinical trial of spironolactone in this population.[10] Using a randomized, double-blind, cross-over design, 10 infants were evaluated during treatment with the combination of chlorothiazide (20 mg/kg twice daily) and spironolactone (1.5 mg/kg twice daily), and again during administration of placebo. Treatment with diuretics for one week produced a significant reduction in mean airway resistance, with an increase in airway conductance and pulmonary compliance, while results for the placebo phase were unchanged. As anticipated, during the diuretic phase, there was also significantly greater urine output, osmolar clearance, and potassium and phosphorus clearance. The authors concluded that diuretics improved lung function in infants with CLD.

Three years later, the same investigators studied the effects of theophylline, with or without diuretics for 4 days, on lung function in 16 infants with CLD.[11] After treatment with diuretics (the same chlorothiazide and spironolactone regimens used earlier), dynamic lung compliance increased, airway resistance decreased and maximal expiratory flow at function residual capacity increased. The combination of diuretics plus theophylline produced an additive benefit on all parameters.

In the April 1989 issue of the *Journal of Pediatrics*, two additional articles were published on diuretic therapy for CLD.[12,13] In the first article, Albersheim and colleagues conducted a randomized, double-blind, placebo-controlled 8-week trial of diuretics in 34 infants with CLD.[13] Patients in the treatment group received hydrochlorothiazide 2 mg/kg and spironolactone 1.5 mg/kg every 12 hours. There were significantly more patients in the treatment group who survived to discharge (84% versus 47% in the controls). There were no significant differences, however, in length of stay or duration of mechanical ventilation. Measurement at 4 weeks revealed a higher total respiratory system compliance with diuretics.

The second article, by Engelhart and colleagues, produced different results.[13] In their trial of 21 infants with CLD, patients were randomized to placebo or a combination of hydrochlorothiazide and spironolactone (3 mg/kg/day of each). Patients were treated for a 6 to 8 day period. Although urine output increased in the treatment group, the authors found no differences in lung mechanics or oxygenation.

In 1994, Kao and colleagues published an additional study to confirm their earlier work.[14] Forty-three infants were randomized to the chlorothiazide and spironolactone combination used in their earlier trials, or placebo, for as long as supplemental oxygen was required. Patients were followed until 1 year of age. Between the first and second pulmonary function tests, the infants in the diuretic group showed significant improvement, while there was no change in the placebo group. By week 4, patients in the diuretic group required less supplemental oxygen; however, there was no difference in the total days of supplemental oxygen required overall between the two groups.

In the most recent study, published in 2000, Hoffman, Gerdes, and Abbasi compared chlorothiazide (20 mg/kg twice daily) to the combination of chlorothiazide and spironolactone (1.5 mg/kg twice daily) for 2 weeks in 33 infants.[15] The addition of spironolactone did not produce an improvement in pulmonary mechanics over thiazide alone and did not reduce the need for electrolyte supplementation.

While the conflicting findings from these studies make interpretation difficult, the results are not surprising. Few pharmacologic therapies have been shown conclusively to affect lung function in neonates with CLD because of the large number of variables affecting outcome. In clinical practice, most institutions continue to use long-term combination diuretic therapy in the management of neonatal CLD.

Use of Spironolactone in Pediatric Heart Disease

Although spironolactone has become a key component in the management of heart failure in infants and children with congenital heart defects, very little has been written about this population.[16-18] In 1980, Baylen and colleagues documented elevated serum aldosterone concentrations in 15 infants with congestive heart failure (average 151±38 ng/dl compared to a mean of 29±7 ng/ml in 20 normal controls).[17] In four of the heart failure patients, spironolactone produced a significant improvement in urine output and a reduction in aldosterone levels.

The following year, Hobbins and colleagues studied spironolactone in 21 infants with congestive heart failure related to congenital heart defects.[18] All patients were already receiving digoxin and chlorothiazide. Ten of the patients were given potassium supplementation, while the remaining 11 were given spironolactone (1 to 2 mg/kg every 12 hours). By the end of one week, bodyweight and liver size

were decreased in the spironolactone group compared to baseline. There were less significant decreases in the potassium patients. The authors concluded that spironolactone produced a clinically significant benefit in their patients on standard therapy for congestive heart failure.

Other Uses in Children

In addition to its use in cardiac and lung diseases, spironolactone has also been used to relieve ascites in children with chronic liver disease.[19] It has also been used to lessen output in patients with protein-losing enteropathies and to reduce potassium loss in children with chronic diarrhea.[20-22] Spironolactone has also been found to be beneficial in juvenile idiopathic arthritis, by inhibiting proinflammatory cytokines.[23]

Pharmacokinetics

The pharmacokinetic profile of spironolactone has not been evaluated in children. In adults, spironolactone has been shown to be well absorbed after oral administration. Food significantly increases its bioavailability and may decrease first-pass metabolism. In a study of nine adults given a single 200 mg oral dose, the maximum serum spironolactone concentration increased from 84±43 ng/ml when fasting to 184±55 ng/ml when given with food.[24]

Spironolactone is highly protein bound (90 to 98%) and has a relatively short elimination half-life (approximately 1.4 hours in adults). It is extensively metabolized to pharmacologically active compounds.[4] Although canrenone was thought for many years to be the primary metabolite produced, more recent research has suggested that 7α-thiomethylspirolactone is formed in greater quantities. Both canrenone and 7α-thiomethylspirolactone, as well as 6β–hydroxy-7α-thiomethylspirolactone have longer elimination half-lives than the parent compound, with average (±SD) values in a study of 12 healthy adult males of 16.5±6.3, 13.8±6.4, and 15.0±4.0 hours, respectively.[25]

Eplerenone reaches peak serum concentrations 1.5 hours after an oral dose. Absorption is unaffected by food. The drug is approximately 50% protein bound, and is metabolized to inactive compounds by cytochrome P450 3A4 (CYP3A4), with a half-life of 4 to 6 hours in adults.[4] As with spironolactone, no pediatric pharmacokinetic studies have been conducted.

Drug Interactions

The most significant drug interactions with the aldosterone inhibitors involve potassium supplements and drugs or foods which alter potassium concentrations. Although these agents are "potassium-sparing," their use in combination diuretic therapy (with a thiazide or loop diuretic) may still result in hypokalemia. In patients on combination therapy who require potassium supplementation, or who are receiving an angiotensin converting enzyme inhibitor, potassium levels should be closely monitored and dosages adjusted to minimize hyperkalemia.[26]

Spironolactone interacts with several other drugs. Cholestyramine may interfere with its absorption; doses of these medications should be separated by at least two hours. The administration of spironolactone with anticoagulants such as warfarin may decrease their efficacy. Spironolactone may decrease the clearance of digoxin, increasing serum digoxin concentrations and potentiating its effects. Eplerenone metabolism is blocked by CYP3A4 inhibitors (eg, azole antifungals, erythromycin, saquinavir, and verapamil), and starting doses should be reduced by 50% in patients on concomitant therapy with one of these agents.[4]

Adverse Effects

The most frequent adverse effects associated with aldosterone inhibitors are electrolyte imbalances, including hyponatremia, hyperkalemia, and hyperchloremic metabolic acidosis. Other less common adverse effects include: drowsiness, headache, lethargy, ataxia, rash, diarrhea, vomiting, abdominal cramps, and gastritis. Rare adverse effects reported with spironolactone include bone marrow suppression, gastrointestinal bleeding, ototoxicity, and nephrocalcinosis. The aldosterone inhibitors have also been shown to produce tumors in rats during chronic toxicity studies, but no cases of cancer have been reported in humans.[4,26]

With prolonged use of spironolactone, up to 10% of patients experience adverse effects from inhibition of testosterone and progesterone, including gynecomastia, impotence, and irregular menses or amenorrhea. These effects are related to both dose and duration of therapy and typically reverse with discontinuation.[4] Eplerenone, with its greater selectivity for aldosterone receptors, has much less potential to cause these effects, and may become the preferred agent for long-term therapy in children.

Availability and Dosing

Spironolactone is available in both brand (Aldactone®; Pfizer) and generic products in 25, 50, and 100 mg tablet strengths.[4] There is no commercially-available oral liquid preparation, but several extemporaneous formulations have been developed.[27]

The recommended dose of spironolactone in infants and children is 1 to 4 mg/kg/day administered as a single dose or in two divided doses. Some references list a dose of 3.3 mg/kg/day, based on conversion of an older recommendation of 1.5 mg/lb/day. In adults, therapy is initiated at 50 to 100 mg/day and titrated up to 400 mg/day as needed. Although some sources recommend twice daily dosing, this regimen does not appear to provide additional benefit over once daily dosing. In a double-blind, cross-over study of 13 adults, spironolactone produced effective blood pressure control and diuresis whether given once or twice daily.[4,28]

Eplerenone (Inspra®; Pfizer) is available as 25, 50, and 100 mg tablets. The usual dose in adults is 50 mg once or twice daily.[4] No dose has been established yet for infants or children.

Summary

With their unique mechanisms of action, the aldosterone inhibitors provide a valuable addition to treatment of children with heart, lung, or renal disease. Although spironolactone has been used successfully for nearly half a century, relatively little has been published on its use in children and much remains to be learned. Eplerenone, with its greater selectivity for aldosterone receptors, may produce fewer adverse effects with long-term use, and should also be studied in the pediatric population.

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