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Hydrocortisone for Refractory Hypotension in Neonates

Marcia L. Buck, Pharm.D., FCCP

Hypotension is a common occurrence in critically ill and preterm neonates. The incidence of hypotension in the preterm neonatal population has been estimated at 20-45% and is inversely proportional to gestational age.^{1,2} Hypotension occurs in approximately 25% of term neonates after surgery for congenital heart defects.³ Management of these patients is difficult, as neonates do not respond to traditional vasopressors. A growing body of literature has suggested that neonatal hypotension is the result of adrenal insufficiency and may be better treated with administration of hydrocortisone. This issue of *Pediatric Pharmacotherapy* will review the basic pharmacology of hydrocortisone and evaluate the recent studies of its use in neonates with hypotension.

Neonatal Steroid Synthesis

Cortisol is one of the body's primary means of counteracting inflammation and maintaining homeostasis. Illness and stress often predispose patients to relative adrenal insufficiency and impaired cortisol response. Neonates, and particularly preterm neonates, may be at greater risk for adrenal insufficiency because of the immaturity of the hypothalamic-pituitary-adrenal (HPA) axis. In utero, the fetus is deficient in 3 β -hydroxysteroid dehydrogenase (3 β HD), and as a result, can produce little cortisol from cholesterol. Instead, cortisol is produced through conversion of placental progesterone by 11 β -hydroxysteroid dehydrogenase (11 β -HSD2), rather than 3 β HD.^{4,5}

After delivery, the neonates' relative inability to produce cortisol de novo may result in a reduced ability to tolerate stress or cardiovascular instability. A number of recent studies have demonstrated depressed levels of both total and free cortisol in preterm neonates, lasting for up to 6 months of life. Conversely, it has been suggested that repeated stress may eventually result in a maladaptive resetting of the HPA axis producing elevated cortisol measured at 8 to 18 months corrected age.⁶

Mechanism of Action

The adrenal insufficiency seen during the neonatal period may result in an excessive inflammatory response to stress. In neonates with hypotension, administration of exogenous corticosteroids may improve blood pressure by minimizing the inflammatory response, inhibiting prostacyclin production and the induction of nitric oxide synthase, as well as stabilizing capillary integrity and upregulating expression of cardiovascular adrenergic and angiotensin type 2 receptors. In addition, corticosteroids increase intracellular calcium availability and decrease reuptake of norepinephrine by inhibition of its metabolism via catechol-O-methyltransferase.^{4,7}

Clinical Trials

Reports of the efficacy of steroids in the management of volume or vasopressor-resistant hypotension in neonates first began to appear in the medical literature in the 1990s.⁸ Within the next couple of years, several retrospective reviews were published which confirmed the beneficial effect. The use of corticosteroids for refractory hypotension was then adopted by many neonatal intensive care units.⁹ Using data from the California Perinatal Quality Care Collaborative, Finer and colleagues found that 12% of the steroid use in the member institutions during the period between April 2002 and March 2003 was for the treatment of hypotension.¹⁰

In the past two years, a number of new studies have been published that further add to our understanding of the role of hydrocortisone in the treatment of neonatal hypotension. The relationship between plasma cortisol levels and response to hydrocortisone was evaluated by Fernandez and colleagues in a retrospective cohort study conducted in 32 preterm infants.¹ Eighteen of the patients had low baseline cortisol levels (< 15 mcg/dL). Twenty-one patients were treated with hydrocortisone, including 18 of the infants with low cortisol levels. Compared to the infants with higher pretreatment cortisol levels, the 18 low-cortisol patients had a greater response to hydrocortisone administration, with a

decrease in the need for dopamine and fluid boluses to maintain adequate blood pressure. The authors concluded that neonates with low baseline cortisol levels were the most likely to benefit from supplemental corticosteroid administration.

Two randomized, double-blind, placebo-controlled studies have also been conducted to evaluate the efficacy of hydrocortisone in the preterm population. Efirid and colleagues randomized 34 patients to receive either hydrocortisone (1 mg/kg every 12 hours for 2 days followed by 0.3 mg/kg every 12 hours for 3 days) or placebo.² Treatment began within the first 3 hours of life. In the first day of life, 25% of the hydrocortisone group required vasopressors to maintain adequate blood pressures, compared to 44% of the placebo group ($p=0.24$). On the second day of life, only 7% of the hydrocortisone group was still receiving vasopressors, compared to 39% of the controls ($p<0.05$). By the 4th day of life, none of the patients required vasopressors. There was one case of gastrointestinal perforation in the hydrocortisone group, but there were no other differences in adverse effects or other outcome measures.

In 2006, Ng and colleagues randomized 48 low birthweight infants with refractory hypotension (requiring dopamine at doses ≥ 10 mcg/kg/min) to receive either hydrocortisone (1 mg/kg every 8 hours) or placebo for 5 days.¹¹ Serum cortisol levels were low prior to treatment in both groups. Significantly more patients treated with hydrocortisone were able to wean off vasopressors within 72 hours (79% versus 33%, $p=0.001$). The cumulative dopamine and dobutamine doses were also significantly less in the steroid-treated group. The trend in mean arterial pressure was also significantly higher in the hydrocortisone group. The authors concluded that hydrocortisone may be a useful addition to the management of refractory hypotension in neonates, but should not be considered for routine or prophylactic therapy because of its potential adverse effects.

Noori and colleagues at the Children's Hospital Los Angeles conducted a prospective observational study in preterm and term neonates with hypotension unresponsive to dopamine.¹² Twenty patients (15 preterm and 5 term) were given hydrocortisone 2 mg/kg IV, followed by four doses of 1 mg/kg every 12 hours. At 48 hours, the dopamine dose had decreased by 72% in the preterm group, with a 31% increase in blood pressure and a 33% increase in stroke volume. Systemic vascular resistance and

cardiac output were also higher after treatment. Contractility, myocardial function, and Doppler studies of cerebral and renal artery blood flow were unchanged. The term infants showed similar results. The authors concluded that hydrocortisone improved blood pressure without compromising cardiac function or impairing cerebral and renal blood flow.

Two studies have been conducted in neonates after surgery to repair congenital heart defects.^{3,7} Ando and colleagues conducted a randomized, placebo-controlled hydrocortisone trial in 20 neonates after open heart surgery.³ Hydrocortisone was administered as an infusion, with a rate of 0.18 mg/kg/hr for 3 days, 0.09 mg/kg/hr for 2 days, and 0.045 mg/kg/hr for 2 days. Treatment was initiated after discontinuation of cardiopulmonary bypass. Cortisol levels were significantly higher in the hydrocortisone group for the first 72 hours after surgery (23.3 ± 7.2 mcg/dL versus 4.6 ± 4.3 mcg/dL in the controls). Patients in the treatment group had an increased left ventricular shortening fraction compared to controls ($p=0.020$), as well as less need for escalation of inotropic support ($p=0.043$), and lower serum lactate values ($p=0.049$). The placebo patients had a greater positive fluid balance ($p=0.027$). Total body edema was greater and duration of mechanical ventilation was longer in the placebo group, but the results were not significantly different.

Suominen and coworkers conducted a retrospective review of 12 neonates treated with hydrocortisone for low cardiac output syndrome following cardiac surgery.⁷ Two regimens were in use over the 2-year observation period: 100 mg/m²/day for 2 days followed by 50 mg/m²/day for 2 days, then 25 mg/m²/day for 1 day or 100 mg/m²/day for 1 day, 50 mg/m²/day for 2 days, then 25 mg/m²/day for 2 days. Mean and systolic blood pressure measurements increased significantly over baseline within 3 hours of hydrocortisone initiation. The mean blood pressure increased from 44.0 ± 3.0 to 55.4 ± 2.3 mm Hg ($p=0.01$). Systolic blood pressure increased from 64.2 ± 4.7 to 78.3 ± 3.4 mm Hg ($p=0.04$). Heart rate also increased and epinephrine was weaned from a mean starting dose of 0.16 mcg/kg/min to 0.06 mcg/kg/min within the first 24 hours of treatment. There were slight increases in blood glucose, white blood cell count, and serum sodium compared to baseline, but none of the differences were statistically significant. Investigators in both of these studies concluded that hydrocortisone was a reasonable adjunct to the management of neonates with refractory hypotension following cardiac surgery.

Adverse Effects

In studies conducted to date in the neonatal population, hydrocortisone has been relatively well tolerated. As in all patients receiving corticosteroids, neonatal patients are at an increased risk for infection, increased intracranial pressure, electrolyte disturbances, hyperglycemia, excessive sodium and fluid retention, impaired wound healing, cutaneous atrophy, cataracts, myopathy, and growth suppression may occur with prolonged use. Hypersensitivity reactions are rare, but may include anaphylactoid reactions with bronchospasm.¹³

Gastrointestinal perforation appears to be one of the primary adverse effects associated with steroid administration in neonates. In 2004, two studies of hydrocortisone for the prevention of chronic lung disease stopped enrollment early because of an increased incidence of gastrointestinal perforation.^{4,14} In their study of hydrocortisone for the prevention of bronchopulmonary dysplasia (BPD), Watterberg and colleagues reported a 12% incidence of gastrointestinal perforation in their patients who received hydrocortisone, compared to 6% rate in the placebo group (adjusted odds ratio 1.98, 95% CI 0.91-4.33).⁴ In the BPD study conducted by Peltoniemi and coworkers, the incidence of perforation was 16% (4/25) in the hydrocortisone group, while none of the 26 controls experience perforation ($p=0.05$).¹⁴ Not all neonatal hydrocortisone studies have reported a greater risk for gastrointestinal perforation. Ng and colleagues reported no difference in the rate of perforation in their treatment group and the controls, despite 79% of the patients having also received indomethacin.¹¹

Unlike dexamethasone, hydrocortisone use has not been associated with neurodevelopmental delay or cerebral palsy.^{10,15-17} This may result from the lower doses of hydrocortisone and shorter duration used in the current studies, as well as the ability of dexamethasone to produce apoptosis and neuronal death in early life, a property not shared by steroids with mineralocorticoid effects such as hydrocortisone.¹⁸ Additional longitudinal studies will be needed to evaluate the long-term effects of hydrocortisone on growth and development.

Drug Interactions

The metabolism of hydrocortisone may be increased by drugs that induce hepatic enzymes, such as carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone, and rifampin. Drugs that inhibit metabolic function, such as itraconazole or ketoconazole, may inhibit

the clearance of hydrocortisone and result in increased serum concentrations. Hydrocortisone should be used with caution in patients receiving warfarin, as the effects on anticoagulation can be variable. Administration of hydrocortisone may increase the clearance of aspirin, reducing its efficacy. Corticosteroids may prolong the effects of neuromuscular blocking agents and should be used with caution in patients requiring pharmacologic paralysis. Although they are not generally used in neonates, fluoroquinolones given concomitantly with corticosteroids may lead to an increased risk for tendon rupture.¹³

In both the Watterberg and Peltoniemi studies described earlier, co-administration with indomethacin or ibuprofen increased the risk for gastrointestinal perforation.^{4,14} There are a number of mechanisms by which non-steroidal anti-inflammatory agents such as indomethacin and ibuprofen produce mucosal damage. Administration of exogenous corticosteroids may produce additive damage by altering local concentrations of growth factors resulting in mucosal hypertrophy and thinning of gastrointestinal smooth muscle.¹⁹ Some investigators have suggested that this may be a dose-dependent effect.⁴

Availability

Hydrocortisone sodium succinate injection is available in 100 mg, 250 mg, 500 mg, and 1,000 mg strengths. Health care providers should be aware that these products may contain benzyl alcohol, which has been associated with the development of cardiovascular collapse, "gaspings syndrome," in premature infants.^{13,20} There is currently a nation-wide shortage of preservative-free hydrocortisone in the United States which is expected for several months.

Dosing Recommendations

A variety of dosage regimens have been used in the hydrocortisone studies conducted to date. In studies of preterm neonates, doses have ranged from 0.5 to 3 mg/kg/day. The most common regimen was 1 mg/kg (approximately 10 mg/m²) every 8 to 12 hours. Hydrocortisone was continued in most of the trials for 3 to 5 days.^{1,2,11,12} In neonates treated for low cardiac output syndrome after surgery, Ando and colleagues used a hydrocortisone infusion of 0.45-0.18 mg/kg/hr and Suominen's group used a dose of 100 mg/m²/day for 1 to 2 days, followed by a taper over the next 4 days.^{3,7}

Hydrocortisone is typically diluted to a concentration of 1 mg/mL prior to administration.^{13,20} It is compatible (at the Y-site) with many medications used in neonates,

including aminophylline, ampicillin, calcium gluconate, cefepime, cisatracurium, dopamine, epinephrine, esmolol, famotidine, fentanyl, furosemide, heparin, insulin, lorazepam, morphine, nicardipine, norepinephrine, pancuronium, piperacillin-tazobactam, vecuronium, and most parenteral nutrition solutions. It is incompatible with diazepam, midazolam, and phenytoin.²¹

Summary

Hydrocortisone may be a useful adjunct to traditional therapies for the treatment of hypotension in neonatal patients. Preliminary studies have demonstrated efficacy and safety in both preterm neonates and neonates undergoing surgery for congenital heart defects. Longitudinal studies are needed to evaluate the long-term effects of hydrocortisone administration on outcome.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/23/07:

1. Sitagliptin (Januvia[™]) was added to the Inpatient and Outpatient Formularies treatment of type 2 diabetes mellitus. It increases the activity of incretin hormones in the gut.
2. Naltrexone (Revia[®]), an opioid receptor site antagonist, was added to the Inpatient Formulary for improving impulse control.
3. The restrictions on celecoxib were amended to include use in patients with hemophilia A or B who have factor X deficiency and patients with aspirin/NSAID allergy or aspirin-intolerant asthma.
4. A request for conivaptan (Vaprisol[®]) was rejected.

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