Evidence-Based Neonatal Pharmacotherapy: Postnatal Corticosteroids

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KEYWORDS

• Dexamethasone • Hydrocortisone
• Bronchopulmonary dysplasia • Cardiovascular insufficiency
• Hypotension • Preterm infant • Newborn infant

ACTIONS OF CORTICOSTEROIDS

Corticosteroids are hormones produced by the adrenal cortex and the synthetic compounds that mimic the actions of those natural hormones. Corticosteroids affect almost all body functions and are therefore among the most powerful agents used in clinical practice. The actions of these hormones can be divided into mineralocorticoid and glucocorticoid actions; however, cortisol, the primary glucocorticoid produced by the adrenal cortex, also has mineralocorticoid actions, as shown in **Box 1**. Cortisol regulates protein, carbohydrate, lipid, and nucleic acid metabolism; maintains cardiac and vascular response to vasoconstrictors; regulates extracellular water and promotes free water excretion; suppresses the inflammatory response and decreases capillary permeability during inflammation; and modulates central nervous system processing and behavior.[1,2] Aldosterone, the primary mineralocorticoid produced in the adrenal cortex, is rarely used as its synthetic equivalent, fludrocortisone, in the neonatal intensive care unit (NICU), and is not discussed in this article.

Synthetic corticosteroids, such as dexamethasone, betamethasone, and prednisone, have variable effects on these multiple functions, differing degrees of mineralocorticoid activity, and widely varying half-lives.[3,4] Thus, determining the relative potency of these different agents can be difficult. Nevertheless, those differences are highly relevant to the actions and effects of the synthetic steroids in clinical practice. For example, dexamethasone has a much longer biologic half-life than cortisol, which may amplify its nominal potency from 25 to 40 times greater than that of hydrocortisone to as much as 150 times higher for some actions.[1,5]

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Box 1
Cortisol actions

Glucocorticoid effects

Regulation of protein, carbohydrate, lipid, and nucleic acid metabolism

Maintenance of cardiac and vascular response to vasoconstrictors

Regulation of extracellular water and promotion of free water excretion

Suppression of the inflammatory response

Lowering of capillary permeability

Modulation of central nervous system processing and behavior

Mineralocorticoid effects

Sodium reabsorption

Potassium excretion

Dexamethasone, the most widely used synthetic steroid in neonatology, has essentially no mineralocorticoid activity but suppresses endogenous cortisol secretion, creating what is sometimes referred to as a *chemical adrenalectomy*.[2,3] This effect, in conjunction with its high potency and long half-life, may help explain the observed adverse effects of dexamethasone on the neurodevelopmental outcomes of preterm infants. The brain contains both mineralocorticoid and glucocorticoid receptors, which are present in particularly high density in the hippocampus, an area of the brain critical to learning and memory.[2,3] At usual physiologic concentrations, cortisol binds primarily to the mineralocorticoid receptors in the brain; only at higher, stress-induced concentrations does it bind substantially to glucocorticoid receptors.[2,3] Because dexamethasone suppresses cortisol secretion, the mineralocorticoid receptors are left unoccupied, leading to neuronal apoptosis in the hippocampus both in vitro and in animal models.[6,7] Administration of corticosterone (the rodent equivalent of cortisol) or aldosterone protects against this apoptosis.[6,7]

Observational human studies have associated impaired learning and memory with smaller hippocampal volumes in children and adolescents born preterm.[8–10] In turn, other observational studies have associated dexamethasone therapy in the preterm infant with smaller brain or hippocampal volumes at term gestation and with adverse neurodevelopmental outcomes.[11–13] Because these observations have not been studied in randomized trials, they may only reflect increased severity of illness in infants who received dexamethasone. However, neither published observational studies nor a preliminary report from a randomized controlled trial (RCT) of hydrocortisone has shown an association between hydrocortisone therapy and decreased hippocampal volume.[14–16] One observational study of approximately 20 infants who were treated with hydrocortisone and had no dexamethasone exposure reported an association between hydrocortisone therapy and decreased cerebellar volume (another area of the brain with high density of corticosteroid receptors). However, the preliminary report from an RCT of hydrocortisone (23 patients treated with hydrocortisone) found no such effect.[16,17]

In addition to differences related to variable mineralocorticoid and glucocorticoid actions and relative potency, corticosteroids have both genomic and nongenomic effects. Genomic actions are those traditionally associated with glucocorticoids, requiring transport to the cell nucleus, transcription, and translation to new protein, with significant time delay to achieve effect (eg, prenatal administration to stimulate