Hydrocortisone

Newborn use only

2022

Alert	Oral dose: Hydrocortisone is not soluble in water and the dose is not evenly distributed in the solution. Refer to preparation section for specific instructions on the oral preparation.
Indication	1. Treatment of cortisol deficiency (hypoadrenalism). 2. Treatment of hypotension NOT responding to inotrope. 3. Short term adjunctive therapy for persistent hypoglycaemia. 4. Prevention of bronchopulmonary dysplasia (not routinely recommended) 5. Adjunct therapy in PPHN secondary to meconium aspiration syndrome.
Action	1. Adrenal corticosteroid with primarily glucocorticoid effects. 2. Enhances vascular reactivity to other vasoactive substances by increasing expression of adrenergic receptors in the vascular wall and increasing calcium concentrations in myocardial cells. 3. Decreases breakdown of catecholamines. 4. Stimulates the liver to produce glucose from amino acids and glycerol and stimulates the deposition of glucose as glycogen.
Drug type	Corticosteroid.
Trade name	IV: Solu-Cortef. Oral: Hysone.
Presentation	100 mg vial, 4 mg tablet, 20mg tablet
Dose	For oral dosing round dose off to the nearest whole milligram (ie round dose off to the nearest half or quarter tablet). **Hypotension (1,2)** ≥ 35 weeks CGA/PMA: 1 mg/kg/dose 6–8 hourly (range 1–2 mg/kg/dose). < 35 weeks CGA/PMA: 1 mg/kg/dose 6–12 hourly (range 1–2 mg/kg/dose). **Hypoglycaemia (3,4)** 1–2.5 mg/kg/dose every 6 hours. **Physiologic replacement (hypoadrenalism) (5)** 8-20 mg/m2/day in 3-4 divided doses. Dosing and dose adjustment should be done in consultation with a Paediatric Endocrinologist. **Stress dose (6,7)** 50 mg/m2/day in 4 divided doses [up to 100 mg/m2/day]. [If length not available use hypoglycaemia dose]. **Body Surface Area (BSA) calculation:** $$BSA\ (m^2) = \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}}$$ **Low dose for prevention of bronchopulmonary dysplasia (not routinely recommended) (8,9)** 0.5 mg/kg/dose every 12 hours for 7 days; then 0.5 mg/kg/dose every 24 hours for 3 days
Dose adjustment	Therapeutic hypothermia : Not applicable ECMO: Not applicable Renal: Not applicable Hepatic: Not applicable
Maximum dose	
Total cumulative dose	
Route	IV, oral.
Preparation	**IV** Add 2 mL of water for injection to the 100 mg vial (50 mg/mL). Draw up 1 mL (50 mg) of reconstituted solution and add 4 mL sodium chloride 0.9% to make a final volume of 5 mL with a concentration of 10 mg/mL. **Oral** Hydrocortisone is not soluble in water. Underdosing or inaccurate dosing can occur when a whole 4mg tablet is dispersed in water, and a proportion of the final volume administered. Doses of hydrocortisone for oral administration should be rounded off to the nearest whole milligram (ie round dose off to the nearest half or quarter tablet).

	Instructions to prepare an oral dose: Using a tablet cutter, cut a 4mg tablet in halves or quarters (depending on the dose required). Crush the portion of tablet required for the dose and disperse it in 1-2mL of sterile water or milk for administration to patient. Discard remaining portion of tablet. Refer to Appendix 1 for instruction sheet for staff and parents.
Administration	IV: Slow IV injection over at least 1 minute. Oral: With feeds.
Monitoring	Measure blood pressure and blood glucose frequently during acute illness. In infants with primary adrenal insufficiency, monitor glucocorticoid replacement by clinical assessment, including growth velocity, body weight, blood pressure and energy levels.
Contraindications	Hydrocortisone is contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.
Precautions	Use of hydrocortisone in preterm infants in the first week is associated with intestinal perforation, particularly when treating concurrently with indomethacin. Untreated systemic bacterial infections. Use with caution in patients with renal impairment, hypothyroidism or cardiac disease. Prolonged use of corticosteroids (> 14 days) may cause prolonged adrenal suppression requiring a tapering dose of hydrocortisone. (6,7.10) Caution should be used when using hydrocortisone for treatment of hyperinsulinaemic hypoglycaemia given the lack of evidence, potential for adrenal suppression and side effects.
Drug interactions	Drugs that induce hepatic enzymes such as phenobarbitone, phenytoin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Increased GI toxicity with concurrent use of indomethacin
Adverse reactions	Hyperglycaemia, glycosuria. Hypertension after 24−48 hours. Vomiting, diarrhoea, gastric irritation, gastrointestinal ulceration and bleeding. Use of hydrocortisone in preterm infants in the first week is associated with intestinal perforation, particularly when treating concurrently with indomethacin. Salt and water retention. Hypokalaemia. Hypocalcaemia and long-term exposure increases the risk of osteopenia. Inhibits immune function and decreases resistance to infection. May mask symptoms of infection. Neutrophilia, thrombocytopenia. Irritability. Acute withdrawal after use > 14 days can lead to acute adrenal insufficiency with fever, hypotension, hypoglycaemia and shock. Long-term use can adversely affect somatic growth.
Compatibility	Fluids: Glucose 5%, glucose 10%, Hartmann's, sodium chloride 0.9% Y-site: Amino acid solutions. Aciclovir, amifostine, aminophylline, anidulafungin, atracurium, atropine, aztreonam, bivalirudin, calcium gluconate, caspofungin, chlorpromazine, cisatracurium, dexamethasone, digoxin, dopamine, doripenem, droperidol, fentanyl, filgrastim, foscarnet, frusemide, granisetron, hyoscine hydrobromide, lignocaine, linezolid, magnesium sulfate, morphine sulfate, neostigmine, noradrenaline, oxytocin, pancuronium, pethidine, piperacillin-tazobactam (EDTA-free), remifentanil, sodium bicarbonate, suxamethonium, vecuronium.
Incompatibility	Fluids: No information. Y-site: Adrenaline hydrochloride, azathioprine, calcium chloride, ciprofloxacin, colistin, dobutamine, dolasetron, ephedrine, ganciclovir, haloperidol lactate, labetalol, midazolam, mycophenolate mofetil, pentamidine, phenobarbitone, promethazine, protamine, rocuronium.
Stability	IV: Reconstituted solution: Stable for 24 hours at 2−8 °C. Protect from light. Diluted solution: Stable for 4 hours below 25 °C or 24 hours at 2−8°C. Oral: Discard remaining pieces of tablet after dose administration.

Storage	Ampoules and tablets: Store below 25°C. Protect from light.
Excipients	Dibasic sodium phosphate, monobasic sodium phosphate
Special comments	Serum cortisol is recommended prior to commencing treatment with hydrocortisone. Caution – Increased risk of GI perforation particularly with simultaneous treatment with indomethacin. If hydrocortisone is required, delay treatment with indomethacin for at least 72 hours if possible. For management of cortisol deficiency, change to oral preparation when possible.
Evidence	**Efficacy:** **Treatment of hypotension:** For primary treatment of hypotension: Hydrocortisone has not been shown to change clinical outcome and may not be as effective as dopamine. (LOE II, GOR D). (1,2) For treatment of refractory hypotension: Hydrocortisone was effective in preventing persistent hypotension. (LOE I, GOR C). Dose range used in trials: 1 to 2.5 mg/kg every 6 to 12 hours weaned over 48 hours to 6 days. (1, 2) There were no statistically significant effects on any other short or long-term outcome but analyses are underpowered to detect differences in clinical and safety outcomes. **Prevention of bronchopulmonary dysplasia:** Trials investigating early use of hydrocortisone in ventilated preterm infants at risk of BPD started hydrocortisone from 2 hours to < 7 days, used various regimens ranging from 0.5 mg/kg/dose 12 hourly for 7 days and 24 hourly for 3 days, 1 to 2 mg/kg every 8 to 24 hours for a duration 2 to 6 days, up to 15 mg/kg x 2 doses.(9,12) Subgroup analysis of trials of hydrocortisone found hydrocortisone was associated with reduced rates of patent ductus arteriosus, mortality, and the combined outcome of mortality or chronic lung disease without increasing the risk of longer-term problems but with increased occurrence of intestinal perforation.(8, 9, 11, 12) Interestingly, in the PREMILOC study baseline serum concentrations of cortisol in the participants did not correlate with BPD free survival.(13) One randomised control trial investigated survival without moderate to severe BPD in 800 preterm infants (GA < 30 weeks) who needed mechanical ventilation for > 7 days after birth. The median age at starting hydrocortisone was 21 days (95% CI: 14 to 28 days). Hydrocortisone was started at 4 mg/kg/day and tapered over 10 days. The study did not find significant difference in either survival without moderate to severe BPD at 36 weeks postmenstrual age or neurodevelopmental impairment at 2 years.(14) Conclusion: Short-term and longer-term effects of early and late hydrocortisone to prevent bronchopulmonary dysplasia require further evaluation. (LOE I, GOR B). (14-17) **Endocrine Society Clinical Practice Guidelines recommend treatment of primary adrenal insufficiency: (5)** Maintenance treatment of primary adrenal insufficiency in children: Hydrocortisone 8 mg/m^2/ day in 3 or 4 divided doses. Management of adrenal crisis: Hydrocortisone 50–100 mg/m^2 IV or IM, then 50–100 mg/m^2 every 24 hours. Home management of illness with fever: Hydrocortisone replacement doses doubled (> 38°C) or tripled (> 39°C) until recovery. Unable to tolerate oral medication due to gastroenteritis or trauma: Hydrocortisone 50 mg/m2 IM. Minor to moderate surgical stress: Hydrocortisone 50 mg/m2 IM or hydrocortisone replacement doses doubled or tripled. Major surgery: Hydrocortisone 50 mg/m2 IV followed by hydrocortisone 50–100 mg/m2/day divided 6 hourly. Acute adrenal crisis: Rapid bolus of normal saline 0.9% 20 mL/kg. Can repeat up to a total of 60 mL/kg within 1 hour for shock. Hydrocortisone 50–100 mg/m2 bolus followed by hydrocortisone 50–100 mg/m2/day divided 6 hourly. Treatment of neonatal hypoglycaemia: There are case reports of short term use of hydrocortisone for neonatal hyperinsulinaemic hypoglycaemia. (3,4) Use of corticosteroids is not addressed in guidelines for management. **Persistent pulmonary hypertension in term neonates** In two retrospective cohort studies use of hydrocortisone in addition to inhaled nitric oxide and inotropes was associated with improved systolic blood pressure and oxygenation. The subgroup of

	infants with meconium aspiration syndrome exhibited decreased need for supplemental oxygen at discharge. (18,19) **Safety:** Use of hydrocortisone in preterm infants in the first week is associated with intestinal perforation. (9,12)(LOE I) The risk may be increased with concomitant treatment with indomethacin. (20,21) (LOE II). Use of hydrocortisone increased risk of hyperglycaemia in hypotensive preterm infants treated with adrenaline. (22) (LOE II). In the PREMILOC study, Early hydrocortisone exposure in extremely preterm infants for prevention of BPD was not associated with either brain lesions at term equivalent age on MRI when adjusted for risk factors, or statistically significant difference in neurodevelopment of participants at 2 years of age. (11, 23). **Pharmacokinetics and pharmacodynamics:** The half-life of hydrocortisone is reported to be < 3 hours in newborn and premature infants. An increase in unbound hydrocortisone clearance was observed at 35 weeks postmenstrual age. (24,25) The pharmacodynamics effect of hydrocortisone on blood pressure in hypotensive preterm infants has been reported to have an onset by 2 hours and persist for at least 12 hours. (26,27)
Practice points	
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