Methylprednisolone
Newborn Use Only

2024

Alert	Routine use of methylprednisolone for prevention of chronic lung disease is not recommended. Do not confuse DEPO-Medrol (methylprednisolone acetate for IM injection only) with SOLU-Medrol (methylprednisolone sodium succinate). In neonates, use sodium succinate salt form only. Some brands and strengths contain benzyl alcohol as the solvent, and not appropriate for neonates. Methylprednisolone sodium succinate and methylprednisolone are equivalent in biological activity and so dosage would be the same.
Indication	Treatment of severe bronchopulmonary dysplasia ≥36 weeks gestation Childhood Interstitial lung disease (ChILD) - As recommended by the paediatric respiratory specialist.
Action	Methylprednisolone is a potent anti-inflammatory steroid. It has a greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention. Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity.
Drug Type	Synthetic glucocorticoid.
Trade Name	Solu-Medrol Powder for injection Act-O-Vial 40 mg/mL, 125 mg/2mL Solu-Medrone 19A (Pfizer, UK) (Echo) Powder for injection 40 mg/mL, 125 mg/2mL Solu-Medrone 19A (Pfizer, UK) Powder for injection 40 mg/mL, 125 mg/2mL **NOTE:** Some brands have other strengths (500mg, 1g and 2g) that contain benzyl-alcohol as the solvent, and not appropriate for neonates. Nursing staff would need to replace the benzyl-alcohol containing solvent with water for injections for the brands containing benzyl alcohol as solvent.
Presentation	Methylprednisolone sodium succinate 40 mg/mL, 125 mg/2 mL.
Dose	**NOTE: To consult paediatric respiratory specialist before commencing methylprednisolone therapy.** 10 mg/kg/day ONCE A DAY for 3 days. Further steroid therapy is in consultation with paediatric respiratory specialist team. Refer to ANMF consensus in evidence section for further information.
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO- No information. Hepatic impairment – No dose adjustment. Renal impairment – No dose adjustment.
Route	IV
Preparation	**<u>Powder for injection Act-O-Vial</u>** 1. Tap to ensure that the powder is at base of the vial and away from the central stopper. 2. Place the Act-O-Vial on a flat, stable surface and hold with one hand. 3. Press down firmly on the plastic activator with the palm of the other hand to force diluent into the lower compartment. 4. Gently mix the solution by turning the vial upside down a number of times. DO NOT SHAKE THE VIAL. 5. Remove plastic tab covering centre of stopper. 6. Sterilise top of stopper with an alcohol swab to prepare for further dilution. **<u>Powder for injection vials</u>** 1. 40 mg vial: Add 1 mL water for injection to the 40 mg vial to make a 40 mg/mL solution. 2. 125 mg vial: Add 2 mL water for injection to the 125 mg vial to make a 62.5 mg/mL solution and further dilute as below. **FURTHER DILUTE BOTH RECONSTITUTED PRODUCTS** 1. <u>40mg/mL solution</u>

	Draw up 1mL from the reconstituted solution and add 7mL sodium chloride 0.9% to make a final volume of 8mL and the final concentration of 5mg/mL. 2. 62.5mg/mL solution Draw up 1mL from the reconstituted solution and add 11.5mL sodium chloride 0.9% to make a final volume of 12.5mL and the final concentration of 5mg/mL.
Administration	Administer over 4-8 hours.[1] Where possible, it is recommended to be administered separately from other medicines or infusion fluids.
Monitoring	Blood pressure, heart rate, and other vital sign monitoring before, during and after infusion. Blood glucose before and 6-8 hourly for 24 hours. Electrolytes as indicated.
Contraindications	Systemic fungal infections Known hypersensitivity to methylprednisolone or to any of the excipients listed.
Precautions	Adrenal suppression Immunosuppression Metabolic bone disease
Drug Interactions	Rota-Virus Vaccine – Risk of rotavirus with live vaccine. Desmopressin – may cause hyponatremia. Fludroquinolones – Risk of tendon rupture. Fentanyl – Risk of withdrawal.
Adverse Reactions	Agitation, gastritis, hyperglycaemia, hypertension, reduced growth (long term treatment), osteopenia (long term treatment), reduced wound healing, hypertrophic cardiomyopathy. Hepatotoxicity, adrenal suppression, infection, sodium and water retention, oedema, hypokalaemia, dyslipidaemia, increased appetite, skin atrophy, bruising, facial flushing, muscle weakness and wasting, cushingoid appearance, weight gain.
Compatibility	**Fluids:**[2] Sodium chloride 0.9%, glucose 5% in sodium chloride 0.45%. **Y site:**[2] Acetaminophen, aciclovir sodium, alfentanil, alprostadil, amifostine, amikacin sulfate, aminocaproic acid, aminophylline, amphotericin B lipid complex, amphotericin B liposome, anidulafungin, ascorbic acid, asparginase, atenolol, atracurium, atropine, azithromycin, aztreonam, bivalirudin, bleomycin, bretylium, buprenorphine, capreomycin, carboplatin, cefamandole, cefazolin, cefepime, cefoperazone, cefotetan, ceftobiprole, ceftriaxone, cefuroxime, cisplatin, clindamycin, cloxacillin, cyanocobalamin, cyclophosphamide, cyclosporine, cytarabine, dactinomycin, daptomycin, dexamethasone sodium phosphate, dexmedetomidine, digoxin, dobutamine, dopamine, doxorubicin, enalaprilat, ephedrine, epoeitin alfa, erythromycin lactobionate, fentanyl citrate, fluconazole, fluorouracil, folic acid, Fosfomycin, fosphenytoin, furosemide, gentamicin, glycopyrrolate, heparin, hydrocortisone sodium succinate, imipenem/cilastatin, insulin, isoproterenol, labetolol, levofloxacin, lidocaine, linezolid, lorazepam, meropenem, meropenem/vaborbactam, Mesna, methadone, methotrexate, metoprolol, metronidazole, milrinone, mivacurium, morphine sulfate, moxifloxacin, multivitamin, nafcillin, naloxone, nitroglycerin, norepinephrine bitartrate, octreotide, pamidronate, pancuronium, penicillin G potassium, penicillin G sodium, pentobarbital, phenobarbital, phenylnephrine, piperacillin, piperacillin/tazobactam, polymyxin B sulfate, potassium acetate, potassium chloride, procainamide, propranolol, remifentanil, sodium acetate, sodium bicarbonate, sodium nitroprusside, streptokinase, succinylcholine, sufentanil, tacrolimus, theophylline, ticarcillin/clavulanate, tobramycin sulfate, tolazoline, valproate sodium, vasopressin, verapamil, vincristine, voriconazole, zolendronic acid.
Incompatibility	**Fluids:**[2] **Caution/variable:** glucose 5%, glucose 5% in sodium chloride 0.9%. **No data:** glucose 10%, sodium chloride 0.45%. **Y site:**[2] **Caution/variable:** Amiodarone, cisatracurium, diltiazem, doxorubicin, esmolol, ketamine, meperidine, midazolam, nicardipine, ondansetron, ticarcillin, tigecycline; **Incompatible:** allopurinol, amphotericin B, ampicillin/sulbactam, calcium chloride, calcium gluconate, caspofungin acetate, cefotaxime, cefoxitin, ciprofloxacin, dantrolene, diazepam, diazoxide, doxycycline, filgrastim, foscarnet, ganciclovir, hydralazine, lansoprazole, leucovorin, magnesium sulfate, minocycline, netilmicin,

	pantoprazole, phenytoin, propofol, protamine, pyridoxine, rocuronium, sulfamethoxazole/trimethoprim, thiamine, vancomycin, vecuronium.
Stability	Reconstitute and dilute immediately before use. Discard any unused solution.
Storage	Store un-reconstituted product below 25°C.
Excipients	Act-O-Vial: Monobasic sodium phosphate, dibasic sodium phosphate, lactose monohydrate, sodium hydroxide. Diluent. Water for injections. Solu-Medrone 19A: Monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, sucrose.
Special Comments	Sodium content: 2mmol/g.
Evidence	**Efficacy** **Bronchopulmonary dysplasia** Bronchopulmonary dysplasia (BPD) in preterm infants is associated with delayed brain maturation and diffuse white matter anomalies that are associated with increased risk of neurodevelopmental impairment.[3] Dexamethasone has been acknowledged in multiple trials as a long-acting glucocorticoid that can be used to prevent or treat developing BPD. Methylprednisolone and prednisolone are alternate steroids, and there is emerging evidence to support their use in some infants at high risk of BPD or established BPD. Methylprednisolone contains glucocorticoid potency similar to prednisolone and can be used in place of prednisolone when an intravenous formulation is in preference. Both prednisolone and methylprednisolone have been safely used for other pulmonary diseases, primarily within the paediatric asthma population, but there is a paucity of available evidence for their use in the neonatal population. Andre et al, studied the benefits and side effects of methylprednisolone in very preterm infants at risk of chronic lung disease in a retrospective comparative study.[4] Forty-five consecutive preterm infants (<30 weeks' gestation) at risk of chronic lung disease were treated at a mean postnatal age of 16 days with a tapering course of methylprednisolone over 9 days. They used methylprednisolone hemisuccinate every 6 hours (0.6, 0.4, 0.2 mg/kg/dose 3 days each). After 9-day therapy, oral betamethasone was given for 21 days on alternated days at a dose of 0.1 mg/kg. The outcome of treatment was assessed by comparison with 45 consecutive historical cases of infants treated with dexamethasone. There were no differences between groups in the rate of survivors without chronic lung disease. Infants treated with methylprednisolone had a higher rate of body weight gain. The incidence of both glucose intolerance requiring insulin and cystic periventricular leukomalacia was lower among methylprednisolone-treated infants. Their observations suggested that methylprednisolone to be as effective as dexamethasone and to have fewer side effects.[4] Dani et al, reported a study primarily focused on the incidence of hypertrophic cardiomyopathy following methylprednisolone therapy.[5] They treated preterm infants on maximal ventilatory and oxygen support with a 12-day tapering course of IV methylprednisolone given every 6 hours (0.6, 0.4, 0.2, 0.1 mg/kg per dose for 3 days each). In this study, there were 10 preterm infants (median gestational age 24 weeks and median birth weight 620 g) affected by respiratory distress syndrome and mechanically ventilated at the median postnatal age of 16.5 days (range: 9–44 days). These infants did not present adverse effects from steroid treatment other than hyperglycaemia (1 case) and hypertrophic cardiomyopathy. Echocardiographic study showed a thickening of the intraventricular septum (40%). No pharmacologic therapy was necessary for these infants. However, methylprednisolone was discontinued immediately (median treatment duration: 8.5 days; range 7–10 days), and the pathologic echocardiographic findings disappeared after a median period of 26 days (range: 22–32 days). Among the methylprednisolone treated infants, 6 (60%) survived, including 3 infants who developed hypertrophic cardiomyopathy.[5] Billion et al, in their retrospective monocentre study, reported 10 preterm infants with severe BPD who received at least one pulse of methylprednisolone (300mg/m²/day IV over three days).[1] Methylprednisolone was given when these infants were dependent on respiratory support for severe BPD at 3 months of age. Each IV dose was given over 4-8 hours. The median number of pulses administered per patient was 2.5, with a minimum of one and a maximum of nine, and the interval

between two pulses was 4 weeks. Methylprednisolone was associated with a decrease in the level of respiratory support, with a greater effect in those on mechanical or non-invasive ventilation.[1]
In a secondary analysis of a multi-centre randomised controlled trial (Preterm Erythropoietin Neuroprotection – PENUT trial), authors reported 2-year neurodevelopmental outcomes in extremely preterm infants treated with dexamethasone, methylprednisolone, and prednisolone. The study identified an association between reduced BSID III scores and > 14 days treatment with dexamethasone. The median (IQR) start day was 29 (20-44) days for dexamethasone and 53 (30-90) days for prednisolone or methylprednisolone. The median (IQR) total days of exposure was 10 (5-15) days for dexamethasone and 13 (6-25) days for prednisolone or methylprednisolone. The median (IQR) cumulative dose of dexamethasone was 1.3 (0.9-2.8) mg/kg. After adjusting for potential confounders, treatment with dexamethasone for longer than 14 days was associated with worse neurodevelopmental outcomes, compared with unexposed infants. The same finding was not identified in the methylprednisolone and prednisolone group however the numbers in this cohort were small (n=99) and brains were more mature at the time of exposure.[6]

Interstitial lung disease in children (child)

Interstitial lung disease in children (chILD) is a rare syndrome that comprises numerous underlying aetiologies. The usual causes of chILD soon after birth are surfactant protein gene mutations, alveolar capillary dysplasia spectrum or preterm babies with respiratory distress which doesn't run the normal clinical course, but the yield of positive results is much less. The chILD-EU collaboration developed consensus guidelines on the diagnosis and initial treatment of chILD. A pulse therapy of 10 mg/kg/day of IV methylprednisolone was suggested in chILD ventilated or close to ventilation. They also suggested doses up to 30 mg/kg/day are used by some centres. The anticipated response rate with this regimen is 7 days.[7]

ANMF consensus: Methylprednisolone is prescribed on a case by case basis for various conditions including severe bronchopulmonary dysplasia. It is to be prescribed only after consultation with relevant subspecialists before commencing therapy. Benefits and safety of IV methylprednisolone are yet to be determined. The published doses of 300-500 mg/m^2/day are derived from small studies and based on expert recommendations and equate to 20-30 mg/kg/day in an average neonate. Until further evidence is available, ANMF consensus is to start with a single IV pulse therapy of 10 mg/kg/day for 3 days in weaning off respiratory support in infants closer to term or post term with severe bronchopulmonary dysplasia, or chILD. If repeat pulses are required, a multidisciplinary team that includes paediatric respiratory physician should assess the need prior to prescribing.

Pharmacokinetics

It is mostly metabolised in liver and excreted in urine, but no specific dose adjustment is suggested.

Safety

Andre et al reported less glucose intolerance and periventricular leukomalacia in infants treated with methylprednisolone in comparison to dexamethasone in their study. In secondary analysis of PENUT trial, dexamethasone for >14 days duration was associated with worse neurodevelopmental outcomes, but no such adverse effect was identified in methylprednisolone or prednisolone group, however numbers were small to draw firm conclusion.[6] Dani et al reported 40% incidence of self-resolving hypertrophic cardiomyopathy in their cohort of infants treated with 12 day tapering course of methylprednisolone.[5]

Vaccines post steroids: Australian Immunisation handbook has made the following recommendations for infants and children weighing ≤10 Kg:[8]

Prednisone-equivalent dose	Duration of therapy	Potential timing of vaccination
<1 mg/kg/day	<30 days	Anytime during therapy
<2 mg/kg/day	<14 days	Anytime during therapy
<2 mg/kg/day	14-28 days	Immunise 1 month before starting corticosteroids or at least 1 month after stopping corticosteroids. Alternatively, person may be able to receive live vaccines at any time during therapy, but only after seeking expert advice.

	≥2 mg/kg/day | <14 days | Immunise 1 month before starting corticosteroids or any time after stopping corticosteroids. ≥2 mg/kg/day | 14-28 days | Immunise 1 month before starting corticosteroids or at least 1 month after stopping corticosteroids. Note: 1 mg prednisone = 1 mg prednisolone = 0.1 mg dexamethasone= 0.8 mg methylprednisolone[9]
Practice points	
References	1. Billion E, Hadchouel A, Garcelon N, Delacourt C, Drummond D. Intravenous pulses of methylprednisolone for infants with severe bronchopulmonary dysplasia and respiratory support after 3 months of age. Pediatr Pulmonol. 2021;56(1):74-82. 2. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: November/29/2023). 3. Anderson PJ, Doyle LW, editors. Neurodevelopmental outcome of bronchopulmonary dysplasia. Semin Perinatol; 2006: Elsevier. 4. Andre P, Thebaud B, Odievre M, Razafimahefa H, Zupan V, Dehan M, et al. Methylprednisolone, an alternative to dexamethasone in very premature infants at risk of chronic lung disease. Intensive care medicine. 2000;26:1496-500. 5. Dani C, Bertini G, Simone P, Rubaltelli FF. Hypertrophic cardiomyopathy in preterm infants treated with methylprednisolone for bronchopulmonary dysplasia. Pediatrics. 2006;117(5):1866-7. 6. Puia-Dumitrescu M, Wood TR, Comstock BA, Law JB, German K, Perez KM, et al. Dexamethasone, prednisolone, and methylprednisolone use and 2-year neurodevelopmental outcomes in extremely preterm infants. JAMA Network Open. 2022;5(3):e221947-e. 7. Bush A, Cunningham S, De Blic J, Barbato A, Clement A, Epaud R, et al. European protocols for the diagnosis and initial treatment of interstitial lung disease in children. Thorax. 2015;70(11):1078-84. 8. Australian Immunisation Handbook. Accessed online on 7 March 2024. 9. Steroid conversion calculator. https://www.mdcalc.com/calc/2040/steroid-conversion-calculator. Accessed on 2 May 2024.

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