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RESEARCH ARTICLE

Clinical Pharmacology of Dexamethasone in Infants and Children

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ABSTRACT

Dexamethasone is a potent glucocorticoid and glucocorticoids are used in the treatment of rheumatic disorders, serious inflammatory rheumatic diseases, vasculitis disorders, Wegener granulomatosis, Churg-Strauss syndrome, nephrotic syndrome, bronchial asthma, other pulmonary diseases, Pneumocystis carinii pneumonia, hypoxia, and inflammation of the eye, inflammatory dermatosis, chronic ulcerative colitis, Crohn disease lymphocytic leukemia, bacterial meningitis, cerebral edema associated with parasites and neoplasm. Dexamethasone accelerates the surfactant production in fetal lung, stabilizes liposomal and cell membranes, inhibits complement-induced granulocyte aggregation, improves alveolar-capillary barrier, inhibits prostaglandin and leukocytes production, decreases pulmonary edema, relaxes bronchospasm, and produces hyperglycemia. In infants, dexamethasone is used to treat bacterial meningitis, hypertension, to facilitate extubation, to treat post-intubation laryngeal edema, croup, and surgical stress. In children, dexamethasone is used to suppress inflammation, to treat allergic disorders, croup, bacterial meningitis, and life-threatening cerebral edema. The effects caused by dexamethasone have been reviewed in infants and children. Dexamethasone is metabolized into 6-hydroxy-dexamethasone and this metabolite is further metabolized into different metabolites. The pharmacokinetics of dexamethasone have been studied in infants and children and the mean elimination half-life is 6.81 h in infants and 2.14–3.06 h in children. The prophylaxis, treatment, and trials with dexamethasone have been reviewed in infants and children. Dexamethasone interacts with drugs, treats bacterial meningitis, and is freely transferred across the human placenta. The aim of this study is to review dexamethasone dosing, effects, pharmacokinetics, prophylaxis, treatment, and trials in infants and children, and dexamethasone metabolism, interaction with drugs, treatment of bacterial meningitis, and placental transfer.

Keywords: Children, dexamethasone, dosing, drug-interaction, effects, infants, meningitis, metabolism, pharmacokinetics, placental-transfer, prophylaxis, treatment, trials

INTRODUCTION

Diagnostic Applications of Dexamethasone

Dexamethasone is a first-line agent to diagnose hypercortisolism, to differentiate among different causes of Cushing syndrome, to determine if patients with clinical manifestations suggestive of hypercortisolism have biochemical evidence of increased cortisol biosynthesis, and an overnight dexamethasone suppression test has been devised. Patients are given 1 mg of dexamethasone orally at 11 pm and cortisol is measured at 8 am the following morning. Suppression of plasma cortisol <1.8 μg/dl strongly suggests that the patient does not have Cushing syndrome. Drugs such as barbiturates that enhance dexamethasone metabolism can interfere with the test. The formal dexamethasone suppression test is used in the differential diagnosis of biochemically documented Cushing syndrome. Following the determination of baseline cortisol levels for 48 h dexamethasone (0.5 mg every 6 h) is administered orally for 48 h. This dose

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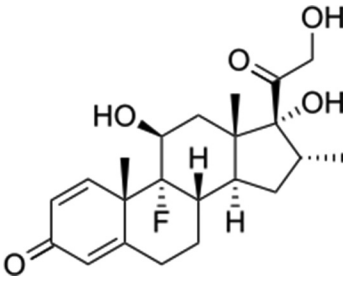
markedly suppresses cortisol levels in normal subjects including those who have the nonspecific elevation of cortisol due to obesity or stress, but it does not suppress cortisol levels in patients with Cushing syndrome. In the high-dose phase of the test, dexamethasone is administered orally at 2 mg every 6 h for 48 h. Patients with pituitary-depended Cushing syndrome (i.e., Cushing disease) generally respond with decreased cortisol levels. In contrast, patients with ectopic production of corticotropin or with adrenocortical tumors generally do not exhibit decreased cortisol levels. Despite these generalities, dexamethasone may suppress cortisol levels in some patients with ectopic production of corticotropin, particularly with tumors such as bronchial carcinoids, and many experts prefer to use inferior petrosal sinus sampling after corticotropin-releasing factor administration to make this distinction.[1]

Clinical Use of Glucocorticoids

Glucocorticoids are used widely in the treatment of rheumatic disorders and are a mainstay in the treatment of more serious inflammatory rheumatic diseases, such as systemic lupus erythematous, and in a variety of vasculitis disorders, such as polyarteritis nodosa, Wegener granulomatosis, Churg-Strauss syndrome, and giant cell arteritis. Patients with nephrotic syndrome secondary to minimal changes in disease generally respond well to steroid therapy, and glucocorticoids are the first-line treatment in both adults and children. Glucocorticoids are used in the treatment of bronchial asthma and other pulmonary diseases. Glucocorticoids are used in patients with AIDS with Pneumocystis carinii pneumonia and moderate-to-severe hypoxia; the addition of glucocorticoids to the antibiotic regimen increases oxygenation and lowers the incidence of respiratory failure and mortality. Glucocorticoids frequently are used to suppress inflammation in the eye and can preserve sight when used properly. Glucocorticoids are remarkably efficacious in the treatment of a wide variety of inflammatory dermatoses. Patients with inflammatory bowel disease (chronic ulcerative colitis and Crohn's disease) may benefit from glucocorticoids. Glucocorticoids are of benefit in autoimmune hepatitis. Glucocorticoids are used in the chemotherapy of acute lymphocytic leukemia and lymphomas because of their antilymphocytic effects, most commonly as a component of combination therapy. Corticoids at very-high doses (e.g., dexamethasone 4 to 16 mg every 6 h) are commonly used in the reduction or prevention of cerebral edema associated with parasites and neoplasm.[1]

Clinical Use of Dexamethasone in Infants and Children

Dexamethasone is a potent glucocorticoid that is well absorbed orally. Because it crosses the placenta, a single course of dexamethasone is widely used to accelerate surfactant production in the fetal lung before birth. Dexamethasone is efficacious in accelerating surfactant production by the preterm fetal lung reducing the risk of death from respiratory distress and many other newborn co-morbidity. The use of dexamethasone to treat chronic lung disease has attracted controversy because of the risk of adverse neurological outcomes in treating preterm infants.[2] Dexamethasone stabilizes lysosomal and cell membranes, inhibits complement-induced granulocyte aggregation, improves the integrity of the alveolar-capillary barrier, inhibits prostaglandin and leukotrienes production, rightward shifts oxygen-hemoglobin dissociation curve, increases surfactant production, decreases pulmonary edema, relaxes bronchospasm. Hyperglycemia is caused by the inhibition of glucose uptake into cells and decreased glucokinase activity. Increased triglyceride synthesis is due to hyperinsulinemia and increased acetyl CoA carboxylase activity. The blood pressure is increased due to increased responsiveness to endogenous catecholamines. Dexamethasone increases protein catabolism with potential loss of muscle tissue, increases urinary calcium excretion because of bone reabsorption, and suppresses pituitary adrenocorticotropic hormone secretion. The elimination half-life is 36–54 h in infants. Dexamethasone is incompatible with glycopyrrolate, midazolam, and vancomycin.[3]



Dexamethasone molecular structure (molecular weight = 392.5 g/mole)

LITERATURE SEARCH

The literature search was performed electronically using the PubMed database as a search engine and the following key words were used: "dexamethasone dosing infants, children," "dexamethasone effects infants, children" "dexamethasone metabolism," "dexamethasone pharmacokinetics infants, children," "dexamethasone prophylaxis infants, children" "dexamethasone treatment infants, children," "dexamethasone trials infants, children," "dexamethasone drug interaction," "dexamethasone meningitis," and "dexamethasone placental transfer." In addition, the books: The Pharmacological Basis of Therapeutics,[1] Neonatal Formulary,[2] NEOFAX by Young and Mangum,[3] and The British National Formulary for Children[4] have been consulted.

RESULTS

Administration Schedules of Dexamethasone to Infants and Children

Administration of dexamethasone to infants.[2]

Prophylaxis with Dexamethasone in Infants

Foetal lung maturation

Give 6 mg of dexamethasone phosphate by intramuscular injection 4 times daily (to a maximum of 24 mg). This can best be achieved by prescribing and administrating the contents of 1.5 ml (4.95 mg) 4 times daily for 4 doses will improve approximately 6 mg dexamethasone phosphate per dose.

Treatment of meningitis

Give 150 μg/kg of dexamethasone base given six hourly given by intravenous or intramuscular injection or by mouth started early can reduce the risk of subsequent deafness in young children with early Hemophilus or pneumococcal meningitis (possibly by moderating toxins from rapid bacterial lysis caused by treatment with cefotaxime).

Treating Chronic Lung Disease

DART trial regimen

Give 60 μg/kg of dexamethasone base twice-daily intravenously (or orally), on days 1–3, 40 μg/kg twice-daily on days 4–6, 20 μg/kg twice-daily on days 7–8, and 8 μg/kg twice-daily on days 9–10 (a total of 712 μg/kg over 10 days). Repeat the dose once if necessary.

Durand trial regimen

Give 100 μg/kg of dexamethasone base intravenously twice-daily for 3 days, and then 50 μg/kg thrice daily for 4 days (a total of 1 mg/kg over 7 days).

Traditional regimen

Give 250 μg/kg of dexamethasone base orally or intravenously twice-daily for 7 days was, until about 10 years ago, the most widely used regimen. Some infants were also offered a second course.

Treating Other Conditions

Treatment of hypertension

Give 100 μg/kg dose followed, if necessary, by 50 μg/kg intravenously twice-daily for 1–2 days often "cures" inotrope-resistant neonatal hypertension.

Facilitating extubation in the preterm infant

Even if the DART regimen (see earlier) does not reduce chronic lung damage, it does facilitate extubation and less than half this dose seemed to help in one small study. The Minidex study used a dose of 50 μg/kg daily for 10 days followed by alternate-day doses for 6 days. The effects of this very low dose have not yet been reported in a randomized trial.

Treatment for post-intubation laryngeal edema

Give three 200 μg/kg doses of dexamethasone base orally or intravenously at eight hourly intervals (started at least 4 and preferably 12 h before the endotracheal tube is removed) may aid extubation in infants and in older children with an edematous or traumatized larynx.

Croup

Viral croup responds to a single 150 μg/kg dose of oral dexamethasone base as well as it does to an intramuscular dose. Effects are seen within 30 min of administration. The dose can be repeated after 12 h if necessary. Inhaled budesonide or oral prednisolone are alternatives with comparable effects.

Surgical stress

To cover possible adrenal suppression, infants on dexamethasone or who last completed a course of dexamethasone lasting more than 1 week <4 weeks previously should receive 1 mg/kg of hydrocortisone intravenously prior surgery and then every 6 h by intravenous or intramuscular injection for 24–48 h.

Administration of Dexamethasone to Children[4]

Oral or by slow intravenous injection for physiologic replacement

Children

Give: 250 to 500 μg/m^2 twice-daily, adjust the dose according to the response.

Oral suppression of inflammatory and allergic disorders

Children

Give: 10–100 μg/kg daily in 1–2 divided doses, adjust the dose according to the responses; up to 300 μg/kg daily may be required in emergencies.

Intramuscular injection or slow intravenous injection or intravenous infusion to suppress inflammatory and allergic disorders

Children aged 1 month–11 years

Give: 83–333 μg/kg daily in 1–2 divided doses (maximum = 20 mg daily).

Children aged 12–17 years

Give: 0.4–20 mg daily.

Oral treatment of mild croup

Children

Give: 150 μg/kg for 1 dose.

Oral treatment of severe croup (or mild croup that might cause complications)

Children

Give initially 150 μg/kg for 1 dose, to be given before transfer to the hospital, and then (by mouth or by intravenous injection) give 150 μg/kg twice-daily, then (by mouth or by intravenous injection) give 150 μg/kg after 12 h if required.

Slow intravenous injection for adjunctive treatment of bacterial meningitis (starting before or with the first dose of antibacterial)

Children aged 3 months to 17 years

Give: 150 μg/kg 4 times-daily (maximum per dose = 10 mg) for 4 days.

Intravenous injection to treat life-threatening cerebral edema

Children with body-weight up to 35 kg

Give initially 16.7 mg, then 3.3 mg 8 times daily for 3 days, then 3.3 mg 4 times-daily for 1 day, then 1.7 mg 4 times daily for 4 days, and then reduce the dose in steps of 0.8 mg daily.

Children with body-weight of 35 kg and above

Give initially 20.8 mg, then 3.3 mg 12 times daily for 3 days, then 3.3 mg 6 times daily, then 3.3 mg 4 times daily for 4 days, and then reduce the dose in steps of 1.7 mg daily.

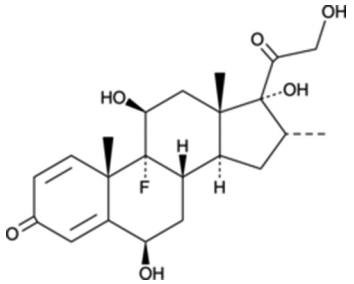
Effects of Dexamethasone in Infants and Children

Administration of antenatal dexamethasone to women at risk for late preterm birth could help to lower the proportion of respiratory distress in late preterm infants.[5] A 3-day course of dexamethasone

administered shortly after birth to preterm infants with respiratory distress syndrome is associated with a significantly increased incidence of cerebral palsy and developmental delay.[6] Dexamethasone reduces T-cell IL-6 and this reduction is associated with improved respiratory severity score in preterm infants with evolving bronchopulmonary dysplasia.[7] Repeat administration of dexamethasone for bronchopulmonary dysplasia is less effective in weaning respiratory support compared to the initial course in children.[8] Antiemetic prophylaxis with fosaprepitant and granisetron with or without dexamethasone is well-tolerated, safe, and effective in pediatric patients.[9] The addition of dexamethasone at a dose of 0.1 mg/kg daily to ropivacaine for the caudal block can significantly improve analgesic efficacy in children undergoing orchiopexy.[10] Neonatal treatment with dexamethasone has long-term consequences for the cardiovascular and noradrenergic stress responses in children at school age.[11] The administration of dexamethasone develops more desirable effects on heart rate and blood oxygen saturation than the administration of lidocaine during postoperative pain.[12] The administration of dexamethasone began before the initiation of cefotaxime therapy providing additional evidence of a beneficial effect of dexamethasone therapy in infants and children with bacterial meningitis.[13] Acute administration of dexamethasone impairs oral glucose tolerance without significantly decreasing insulin sensitivity.[14]

Metabolism of Dexamethasone

Dexamethasone is extensively metabolized into 6-hydroxy-dexamethasone and side-chain cleaved metabolites in the human liver both *in-vitro* and *in-vivo* with CYP3A4 responsible for the formation of 6-hydroxylated products.[15] The metabolism of dexamethasone was studied in-vitro using human liver microsomes. A total of 17 human livers were used and the following metabolites were identified: 6-β-hydroxy-dexamethasone, 6-α-hydroxy-dexamethasone, 6-hydroxy-9-α-fluoro-androsta-1,4-diene-11-β-hydroxy-16 α-methyl-3,17-dione, and 9-α-fluoro-androsta-1,4-diene-11 β-hydroxy-16 α-methyl-3,17-dione. Dexamethasone underwent side-chain cleavage to form β-hydroxy-16 α-methyl-3,17-dione. This metabolite was then a substrate for 6-hydroxylation. There was considerable interindividual variability in metabolic profiles. Km values for 6 β- and 6 α-hydroxy-dexamethasone formation were 23.2 ± 3.8 and 25.6 ± 1.6 μM (n = 4), respectively. The corresponding Vmax values were 14.3 ± 9.9 and 4.6 ± 3.1 pmol/min/mg protein. Ketoconazole (3 μM) completely inhibited 6 α- and 6 β-hydroxylation, indicating that the formation of both metabolites was catalyzed by CYP3A4. This was confirmed in studies of correlations between the rate of metabolite formation and the relative expression of CYP3A4 (r = 0.74) for 6 β-hydroxy-dexamethasone (P = 0.003; r = 0.70) and for 6 α-hydroxy-dexamethasone (P = 0.006).[16]



6-Hydroxy dexamethasone molecular structure (molecular weight = 408.46 g/mole)

Pharmacokinetics of Dexamethasone in Infants

Lugo *et al*.[17] studied the pharmacokinetics of dexamethasone in 15 preterm infants with postmenstrual age, postnatal age, and body weight of 28.0 ± 0.6 weeks, 28.3 ± 5.8 days, and 1,188 ± 267 kg, respectively, and dexamethasone was intravenously infused at a dose of 0.30 ± 0.03 mg/kg. Table 1 summarizes the pharmacokinetic parameters of dexamethasone.

This table shows that the distribution volume of dexamethasone is greater than the water volume, dexamethasone is slowly eliminated as the mean elimination half-life is 6.81 h, and there is a remarkable interindividual variability in the pharmacokinetic parameters. This variability may be accounted for by a wide variation in demographic characteristics of the infants included in the study. In addition, there is a significant correlation between the total body clearance of dexamethasone and the postmenstrual age (r = 0.884, P = 0.002) and the total body clearance of dexamethasone and the postnatal

age ($r = 0.741$, $P = 0.022$). The more premature infants have a significantly lower total body clearance than less premature infants (1.69 ± 0.79 versus 7.57 ± 3.71 ml/min/kg, $P = 0.018$). The distribution volume of dexamethasone correlates with the postmenstrual age ($r = 0.847$, $P = 0.004$) and the distribution volume of dexamethasone correlates with the body weight ($r = 0.830$, $P = 0.006$).

Pharmacokinetics of Dexamethasone in Children

Yang *et al*.[18] studied the pharmacokinetics of dexamethasone in 165 children aged 1.9–9.2 years (Study 1) and in 49 children aged 10.0–18.8 years (Study 2) and dexamethasone was administered intravenously at a dose of 2.67 mg/m^2. Table 2 summarizes the pharmacokinetic parameters of dexamethasone.

This table shows that the distribution volume of dexamethasone is larger than the water volume, the total body clearance is greater in younger than in older children, and dexamethasone is rapidly eliminated as the mean elimination half-life ranges from 2.14 to 3.06 h. The elimination half-life of dexamethasone obtained in children is shorter than that obtained in infants (for infants see Table 1). Dexamethasone is cleared from the body by metabolism and by renal route and both elimination pathways increase with infant maturation and child development. The comparison of the total body clearance and the distribution volume obtained in children cannot be compared to those obtained in infants because both parameters are expressed in different unities in infants and children.

Prophylaxis with Dexamethasone Infants and Children

Dexamethasone is the most appropriate postnatal corticosteroid regimen for preventing bronchopulmonary dysplasia and mortality rate in preterm infants.[19] Administration of dexamethasone before extubation significantly reduced the need for reintubation of the trachea in infants.[20] There is a trend towards a reduced incidence of reintubation in infants receiving prophylactic dexamethasone before extubation.[21] Intravenous dexamethasone has a beneficial effect in children with sickle cell disease and causes mild to moderately severe acute chest syndrome.[22] Dexamethasone is effective in preventing reintubation due to post-extubation stridor in high-risk infants and children.[23] Prophylactic administration of dexamethasone before elective extubation reduces the prevalence of post-extubation stridor in infants and children and may reduce the rate of reintubation.[24] Prophylactic use of intravenous dexamethasone is useful in preventing

Table 1: Pharmacokinetic parameters of dexamethasone which have been obtained in 15 preterm infants and dexamethasone was intravenously infused at a dose of 0.30±0.03 mg/kg

Value	Peak Conc. (ng/ml)	Cmin (ng/ml)	TBC (ml/min/kg)	DV (L/kg)	*Half-life (h)
Minimum	117	5.5	1.03	1.0	2.2
Maximum	462	182	8.60	2.36	15.8
Mean	227	76.3	5.00	1.80	6.81
+SD	38	20.0	1.40	0.17	1.43

Values are the minimum, the maximum, and the mean±SD, by Lugo *et al*.[17] Cmin: Minimum plasma concentration, TBC: Total body clearance, DV: Distribution volume, *Elimination half-life

Table 2: Pharmacokinetic parameters of dexamethasone which have been obtained in 165 children aged 1.9–9.2 years (Study 1) and in 49 children aged 10.0–18.8 years (Study 2)

Number of children	Age range (years)	Dose (mg/m^2)	Total body clearance (L/h/m^2)	Distribution volume (L/m^2)	Elimination half-life (h)
Study 1					
165	1.9–9.2	2.67	15.5±0.7	47.9±1.5	2.14±0.14
Study 2					
49	10.0–18.8	2.67	9.78±0.76	42.9±2.59	3.06±0.14

Dexamethasone was administered intravenously at a dose of 2.67 mg/m^2. Values are the mean±SD, by Yang *et al*.[18]

post-extubation laryngeal enema and stridor in children.[25] Prophylactic dexamethasone reduces the prevalence of post-extubation stridor in infants and children.[26]

Treatmentof Infants and Children with Dexamethasone

Intravenous dexamethasone is effective in treating bronchopulmonary dysplasia in preterm infants.[27] Dexamethasone has powerful anti-inflammatory effects and has been used to treat established bronchopulmonary dysplasia in preterm infants.[28] A 42-day course of dexamethasone therapy beginning at 2 weeks of age in preterm infants who are at high-risk for severe chronic lung disease is associated with improved long-term neurodevelopmental outcomes.[29] The beneficial effects of short-term inhaled dexamethasone on the resistive airflow properties of preterm infants at risk for bronchopulmonary dysplasia may provide adjunctive means to facilitate weaning in the ventilator-dependent infants.[30] The administration of low-dose of dexamethasone after the 1st week of life facilitates extubation and shortens the duration of intubation in preterm infants.[31] Early dexamethasone treatment reduces the mortality rate and the combined outcome of mortality and bronchopulmonary dysplasia without increasing the risk of adverse neurodevelopmental outcomes in ventilated preterm infants.[32] Dexamethasone improves the pulmonary function of preterm infants with bronchopulmonary dysplasia.[33] Dexamethasone therapy for 42 days improves pulmonary and neurodevelopmental outcomes in preterm infants at high risk for bronchopulmonary dysplasia.[34] Treating infants with bronchiolitis with a combination of nebulized epinephrine plus oral dexamethasone is the most cost-effective treatment option because it is the most effective in controlling symptoms and is associated with the least costs.[35] Clinical improvement of signs of meningeal irritation is more rapid in the dexamethasone group than in the placebo group in children but no significant difference was observed regarding resolution of fever, headache, and vomiting.[36] Dexamethasone administration in addition to antimicrobial therapy is effective in reducing neurologic sequelae and bilateral hearing loss associated with bacterial meningitis in children.[37] Dexamethasone is recommended in infants and children aged >2 months with suspected bacterial meningitis because it reduces the incidence of meningitis-induced hearing loss.[38]

Trials with Dexamethasone in Infants and Children

Dexamethasone affects the intelligence of preterm infants in the early stages after birth and leads to hearing impairment at later stages after birth.[39] Higher cumulative dexamethasone doses administered after the first week of life may decrease the risk for bronchopulmonary dysplasia without increasing the risk for neurodevelopmental sequelae in ventilated preterm infants.[40] In preterm infants with severe respiratory distress syndrome requiring assisted ventilation shortly after birth, early postnatal dexamethasone therapy reduces the incidence of chronic lung disease, probably based on decreasing the pulmonary inflammatory process during the early neonatal period.[41] Early therapy with dexamethasone in very-low-birth-weight infants markedly improves respiratory compliance and tidal volume, reduces the fractional inspired oxygen concentration, the mean airway pressure requirements facilitates extubation, decreases the duration of mechanical ventilation, and chronic lung disease.[42] In children undergoing adenotonsillectomy, dexamethasone decreases the early postoperative pain and postoperative nausea and vomiting without increasing postoperative hemorrhage.[43] Two doses of 0.6 mg/kg of dexamethasone are an effective alternative to a 5-day course of 1.5/1 mg/kg prednisone/prednisolone for treatment of asthma exacerbations in children as measured by the persistence of symptoms and quality of life at day 7 of treatment.[44] Dexamethasone therapy for 2 days treats childhood meningitis caused by hemophilus meningitis if commenced with or before parenteral antibiotics and suggests benefit for pneumococcal meningitis in childhood.[45] Prophylactic administration of multiple-doses of dexamethasone is effective in reducing the incidence of post-extubation stridor in pediatric

patients at high risk for post-extubation laryngeal edema.[46] Pre-treatment with dexamethasone at a dose of 0.5 mg/kg (maximum dose = 10 mg) decreases the frequency of post-extubation airway obstruction in children.[47]

Interaction of Dexamethasone with Drugs

Dexamethasone can increase CYP3A4 activity by up to 70% and reduce the area under the concentration-time curve of CYP3A4 substrates by >40%, which is consistent with the criteria for a weak CYP inducer. The concurrent use of dexamethasone and apixaban or rivaroxaban in COVID-19 patients carries the potential for reduced anticoagulant effect during a state of heightened thrombotic risk.[48] Co-administration of dexamethasone with oseltamivir slightly decreases systemic exposure to oseltamivir and oseltamivir carboxylate in healthy volunteers.[49] Dexamethasone is an inducer of CYP3A4 and this CYP metabolizes triazolam thus dexamethasone reduces the plasma concentration of triazolam.[50] The serum phenytoin concentration is 17.28 ± 3.49 μg/ml in patients receiving dexamethasone and phenytoin as compared to 12.48 ± 3.52 μg/ml in patients receiving only phenytoin ($P < 0.001$). Thus dexamethasone increases the serum concentration of phenytoin. These results suggest that serum phenytoin concentrations should be monitored in patients receiving concurrent dexamethasone therapy.[51]

Treatment of Bacterial Meningitis with Dexamethasone

Pediatric patients with purulent meningitis caused by *Staphylococcus epidermis* or by *Streptococcus pneumoniae* are resistant to levofloxacin while the auxiliary medication of dexamethasone can improve the efficacy and inhibits the inflammation.[52] The use of dexamethasone as adjunctive therapy in invasive meningococcal meningitis has a degree of proven benefits and no harmful effects. In meningococcal meningitis, dexamethasone is recommended as adjunctive treatment.[53] Early treatment with dexamethasone improves the outcome in children with acute bacterial meningitis and does not increase the risk of gastrointestinal bleeding.[54] Dexamethasone treats infants and children with meningitis caused by *S. pneumoniae* or by *Neisseria meningitis*.[55] Dexamethasone therapy initiated just before or simultaneously with the first parenteral antibiotic dose is recommended in infants and children with bacterial meningitis.[56] Treatment with dexamethasone administered intravenously at a dose of 0.4 mg/kg daily combined with ceftriaxone administered intravenously at a dose of 100 mg/kg daily improves outcomes from bacterial meningitis in infants and children.[57] Children with meningococcal meningitis were treated intravenously with conventional antimicrobial therapy and were randomly assigned to receive dexamethasone intravenously at a dose of 0.15 mg/kg 4 times daily for 2 or 4 days. The clinical response was similar for both dexamethasone regimens and children survived without neurologic or audiological sequelae.[58] Dexamethasone administered intravenously at a dose of 0.15 mg/kg 4 times daily for 4 days effectively treats infants and children with bacterial meningitis presents deafness and infants and children became afebrile after 2 days of treatment.[59] Children with meningitis caused by *Haemophilus influenzae* were treated with dexamethasone and with standard antibiotics. The addition of dexamethasone to standard antibiotic treatment improves the outcome of children admitted to hospital with a diagnosis of bacterial meningitis.[60] Children with bacterial meningitis were treated with ceftriazone plus dexamethasone intravenously. Dexamethasone improves the inflammatory reaction in acute bacterial meningitis and shortened the duration of fever.[61]

Transfer of Dexamethasone Across the Human Placenta

The transfer of dexamethasone cross the human placenta was studied in twin fetuses and in a singleton fetus. The mean of the umbilical cord vein serum to the maternal vein serum ratio is significantly lower in twin fetuses than in singleton fetus (0.36 vs. 0.56, $P = 0.007$).[62] The transfer of dexamethasone across the human term placenta was studied using placental perfusion.

Dexamethasone crosses the human placenta and the concentration of dexamethasone is greater in the fetal vein serum than in the maternal vein serum suggesting that dexamethasone freely crosses the human placenta.[63]

DISCUSSION

Dexamethasone is a potent glucocorticoid. Glucocorticoids are widely used in the treatment of rheumatic disorders and in the treatment of more serious inflammatory rheumatic disorders such as systemic lupus erythematous, and in a variety of vasculitis disorders such as the polyarteritis nodosa, Wegener granulomatosis, Churg-Strauss syndrome, and giant cell arteritis. Glucocorticoids are the first-line treatment of adults and children with nephrotic syndrome and are used in the treatment of bronchial asthma, other pulmonary diseases, in patients with AIDS with Pneumocystis carinii pneumonia, and moderate-to-severe hypoxia, in treatment of eye inflammation, inflammatory dermatosis, inflammatory bowel disease (chronic ulcerative colitis and Crohn disease), autoimmune hepatitis, in the chemotherapy of acute lymphocytic leukemia, and lymphomas because of their anti lymphocytic effects. A high dose of dexamethasone (4–16 mg every 6 h) is used in reducing or preventing cerebral edema associated with parasites and neoplasm.[1] Dexamethasone is well absorbed orally and because it crosses the placenta a single course of dexamethasone is widely used to accelerate the production of surfactant in the fetal lung before birth. Dexamethasone accelerates the surfactant production in the preterm foetal lung reducing the risk of death from respiratory distress and much other newborn co-morbidity.[2] Dexamethasone stabilizes lysosomal and cell membranes inhibits complement-induced granulocyte aggregation, improves the integrity of the alveolar-capillary barrier, inhibits prostaglandin and leukotrienes production, rightward shifts oxygen-hemoglobin dissociation curve, increases surfactant production, decreases pulmonary edema, relaxes bronchospasm, inhibits the uptake of glucose into the cells and thus causes hyperglycemia. The increase of triglyceride synthesis is due to hyperinsulinemia and increased acetyl CoA carboxylase synthesis. Dexamethasone increases blood pressure due to an increased responsiveness to endogen catecholamines, protein catabolism with potential loss of muscle tissue, urinary calcium excretion, and suppresses pituitary adrenocorticotropic hormone secretion. In infants, the elimination half-life of dexamethasone is 36–54 h.[3] The dosing of dexamethasone has been reviewed in infants[2] and in children.[4] The effects of dexamethasone have been reviewed in infants and children. The administration of antenatal dexamethasone to pregnant women at risk for late preterm birth reduces the proportion of respiratory distress in late preterm infants.[5] A three-day courses of dexamethasone administered shortly after birth to preterm infants with respiratory distress syndrome increase the incidence of cerebral palsy and development delay,[6] dexamethasone reduces T-cell IL-6 and this reduction improves respiratory severity score in preterm infants with evolving bronchopulmonary dysplasia,[7] repeat administration of dexamethasone for bronchopulmonary dysplasia is less effective in weaning respiratory support compared to initial course in children.[8] Antiemetic prophylaxis with fosaprepitant and granisetron with or without dexamethasone is safe and effective in pediatric patients.[9] Dexamethasone (0.1 mg/kg daily) added to ropivacaine for the caudal block can improve the analgesic effect in children undergoing orchiopexy.[10] Neonatal treatment with dexamethasone causes long-term consequences for the cardiovascular and noradrenergic stress responses in children.[11] Dexamethasone develops more desirable effects on heart-rate and blood oxygen saturation than lidocaine during postoperative pain,[12] dexamethasone administration began before the initiation of cefotaxime therapy has a beneficial effect in infants and children with bacterial meningitis,[13] and acute administration of dexamethasone impairs oral glucose tolerance without decreasing insulin sensitivity.[14] These results indicate that dexamethasone causes different effects in infants and children. The metabolism of dexamethasone has been studied *in-vitro* in human liver and *in-vivo* in humans. Dexamethasone is metabolized into 6-hydroxy-dexamethasone and side-chain cleaved metabolites in the human liver

both *in-vitro* and *in-vivo* with CYP3A4 responsible for the formation of 6-hydroxylated products.[15] The metabolism of dexamethasone was studied in-vitro using specimens of 17 human livers, dexamethasone is extensively converted into different hydroxylated metabolites and there is a considerable interindividual variability in the metabolic profiles. The hydroxylation of dexamethasone is inhibited by ketoconazole indicating that dexamethasone is hydroxylated by CYP3A4.[16] These results indicate that dexamethasone is extensively metabolized *in-vitro* in human liver and *in-vivo* in humans. The pharmacokinetics of dexamethasone has been studied in preterm infants and in children and the mean elimination half-life is 6.81 ± 1.43 h in preterm infants[17] and 2.14 ± 0.14–3.06 ± 0.14 h in children.[18] Dexamethasone is cleared from the body by metabolism and by the renal route and both elimination pathways increase with infant maturation and child development thus the elimination half-life of dexamethasone is longer in infants than in children. The prophylaxis with dexamethasone has been reviewed in infants and children. Dexamethasone is the most appropriate corticosteroid for the prevention of bronchopulmonary dysplasia and mortality-rate in preterm infants,[19] dexamethasone administered prior extubation reduces the need for reintubation of trachea in infants,[20] dexamethasone reduces the incidence of reintubation in infants prior to extubation,[21] intravenous dexamethasone has a beneficial effect in children with sickle cell disease and causes mild to moderately severe chest syndrome,[22] dexamethasone effectively prevents reintubation due to post-extubation stridor in high-risk infants and children,[23] prophylactic administration of dexamethasone before elective extubation reduces the prevalence of post-extubation stridor in infants and children and may reduce the reintubation-rate,[24] prophylactic use of intravenous dexamethasone prevents post-extubation laryngeal enema and stridor in children,[25] and prophylactic dexamethasone reduces the prevalence of post-extubation stridor in infants and children.[26] These results indicate that prophylaxis with dexamethasone prevents different diseases and reduces the prevalence of post-extubation stridor in infants and children.The treatment of infants and children with dexamethasone has been reviewed. Dexamethasone effectively treats bronchopulmonary dysplasia in preterm infants,[27] and dexamethasone has powerful anti-inflammatory effects and treats bronchopulmonary dysplasia in preterm infants.[28] A 42-day course of dexamethasone therapy began at 2 weeks of age in preterm infants who are at high risk of chronic lung disease improves long-term neurodevelopment outcomes,[29] and short-term inhaled dexamethasone reduces resistive airflow properties in preterm infants with bronchopulmonary dysplasia and facilitates weaning in ventilated infants.[30] The administration with low-dose of dexamethasone after the first week of life facilitates the extubation and shortens the duration of intubation in preterm infants,[31] early dexamethasone treatment reduces the mortality-rate and bronchopulmonary dysplasia without increasing the risk of adverse outcome in preterm infants,[32] dexamethasone improves pulmonary function in preterm infants with bronchopulmonary dysplasia,[33] dexamethasone administered for 42 days improves pulmonary and neurodevelopmental outcome in preterm infants who are at high-risk for bronchopulmonary dysplasia,[34] the combination of nebulized epinephrine with oral dexamethasone effectively treats bronchiolitis in infants,[35] dexamethasone treats meningeal irritation in children more rapidly than placebo but no significant difference was observed regarding the resolution of fever, headache, and vomiting,[36] dexamethasone co-administered to antimicrobial therapy effectively reduces neurologic sequelae and bilateral hearing loss in children with bacterial meningitis,[37] and dexamethasone is recommended in infants and children aged >2 months with bacterial meningitis because it reduces the incidence of meningitis-induced hearing loss.[38] These results indicate that dexamethasone treats different diseases in infants and children. The trials with dexamethasone have been reviewed in infants and children. Dexamethasone affects the intelligence of preterm infants soon after birth and leads to hearing impairment at later stages after birth.[39] High cumulative doses of dexamethasone administered soon after birth decreases the risk of bronchopulmonary dysplasia without increasing the

risk of neurodevelopment sequelae in preterm infants.[40] Dexamethasone therapy initiated early after birth reduces the incidence of chronic lung disease in preterm infants and decreases the pulmonary inflammatory process.[41] Treatment with dexamethasone initiated early after birth improves respiratory compliance and tidal volume, reduces the fractional inspired oxygen concentration, the mean airway pressure requirements, facilitates extubation, and decreases chronic lung disease in very low-birth-weight infants.[42] Dexamethasone decreases the early postoperative pain, postoperative nausea, and vomiting without increasing postoperative hemorrhage in children undergoing adenotonsillectomy.[43] Two doses of 0.6 mg/kg of dexamethasone are effective as a 5-day course of 1.5/1 mg/kg of prednisone/prednisolone in the treatment of asthma exacerbations in children as measured by the persistence of symptoms and quality of life at day 7 of treatment.[44] Dexamethasone therapy for 2 days treats childhood meningitis caused by Haemophilus meningitis if commenced with or before parenteral antibiotics.[45] Prophylactic administration of multiple doses of dexamethasone effectively reduces the incidence of post-extubation stridor in pediatric patients at high risk for post-extubation laryngeal edema.[46] Pre-treatment with dexamethasone at a dose of 0.5 mg/kg (maximum dose = 10 mg) decreases the frequency of post-extubation airway obstruction in children.[47] These results indicate that dexamethasone treats different diseases in infants and children. Dexamethasone interacts with drugs. Dexamethasone is an inducer of CYP3A4 and the concurrent use of dexamethasone with apixaban or rivaroxaban in COVID-19 patients carries the potential for reduced anticoagulant effect during a state of heightened thrombotic risk.[48] The co-administration of dexamethasone with oseltamivir slightly decreases systemic exposure to oseltamivir and oseltamivir carboxylate in healthy volunteers.[49] Dexamethasone is an inducer of CYP3A4 and this CYP metabolizes triazolam thus dexamethasone reduces the plasma concentration of triazolam.[50] Dexamethasone increases the serum concentration of phenytoin and the serum phenytoin concentrations should be monitored in patients receiving concurrent dexamethasone therapy.[51] These results indicate that dexamethasone interacts with drugs. The treatment of bacterial meningitis with dexamethasone has been reviewed in infants and children. Paediatric patients with purulent meningitis caused by *Staphylococcus epidermidis* or by *Streptococcus pneumoniae* are resistant to levofloxacin and while the auxiliary medication of dexamethasone can improve the efficacy and inhibit the inflammation.[52] Dexamethasone is recommended as adjunctive treatment in invasive meningococcal meningitis.[53] Early treatment with dexamethasone improves the outcome in children with acute bacterial meningitis and does not increase the risk of gastrointestinal bleeding.[54] *Streptococcus pneumoniae* or by *Neisseria meningitis* in infants and children.[55] Dexamethasone therapy initiated before or simultaneously with a parenteral antibiotic is recommended in infants and children with bacterial meningitis.[56] Dexamethasone administered intravenously at a dose of 0.4 mg/kg daily combined with intravenous ceftriaxone at a dose of 100 mg/kg daily improves bacterial meningitis outcomes in infants and children.[57] Dexamethasone administered intravenously at a dose of 0.15 mg/kg 4 times daily for 2 or 4 days treats meningitis caused by *Haemophilus influence* or by *Meningococcal meningitis* in children who survived without neurologic or audio logical sequelae.[58] Dexamethasone administered intravenously at a dose of 0.15 mg/kg 4 times daily for 4 days effectively treats bacterial meningitis in infants and children who became afebrile after 2 days of treatment and this treatment prevents deafness.[59] The co-administration of dexamethasone with standard antibiotic treatment improves the outcome of children admitted to hospital with meningitis caused by *Haemophilus influenzae*.[60] Dexamethasone plus ceftriaxone administered intravenously to children improves the inflammatory reaction in acute bacterial meningitis and shortness of the duration of fever.[61] The transfer of dexamethasone across the human placenta was studied in twin fetuses and in single fetus and the mean of the umbilical cord vein serum to the maternal vein serum ratio is significantly lower in twin fetuses than in single fetus.[62] The transfer of

dexamethasone across the human placenta was studied using placenta perfusion. Dexamethasone crosses the placenta and the concentration of dexamethasone is greater in the fetal vein serum than in the maternal vein serum suggesting that dexamethasone freely crosses the human placenta.[63]

CONCLUSION

In conclusion, dexamethasone is a potent glucocorticoid and may be administered orally or intravenously, and after oral dosing dexamethasone is rapidly absorbed. In infants, dexamethasone is used to improve fetal lung maturation, to treat bacterial meningitis, chronic lung disease, and hypertension, to facilitate extubation, to treat post-intubation laryngeal edema, croup, and surgical stress. In children, dexamethasone is used to suppress inflammatory and allergic disorders, to treat mild and severe croup, bacterial meningitis, and life-threatening cerebral edema. The effects of dexamethasone have been extensively reviewed in infants and children and dexamethasone is metabolized into 6-hydroxy-dexamethasone by CYP3A4 and this metabolite is further metabolized into different metabolites. The pharmacokinetics of dexamethasone has been studied in infants and children and the mean elimination half-life of dexamethasone is 6.81 h in infants and 2.14–3.06 h in children. Dexamethasone is cleared from the body by metabolism and by the renal route and both elimination pathways increase with infant maturation and child development thus the elimination half-life of dexamethasone is longer in infants than in children. The prophylaxis, treatment, and trials with dexamethasone have been extensively reviewed in infants and children. Dexamethasone interacts with drugs, treats bacterial meningitis, and is freely transferred across the human placenta. The aim of this study is to review the clinical pharmacology of dexamethasone in infants and children.

CONFLICT OF INTERESTS

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria. This article is a review and drugs have not been administered to men or animals.

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