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Clinical Pharmacology of hydrocortisone in infants and children

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Abstract

Hydrocortisone may be administered intravenously, orally, or topically and hydrocortisone is well absorbed after oral or topical administration. In infants, hydrocortisone has been used to treat hypotension, to prevent and treat bronchopulmonary dysplasia, to treat congenital adrenal hypertension, adrenal hypoplasia, and Addisonian crisis. In children, hydrocortisone has been used to treat acute adrenal insufficiency (Addison crises), congenital adrenal hyperplasia, adrenal hypoplasia, inflammatory bowel disease, ulcerative colitis, proctosigmoiditis, acute hypersensitivity reactions, angioedema, hypotension, severe acute asthma, and life-threatening acute asthma. The efficacy and safety of hydrocortisone have been studied in infants and children. Hydrocortisone has been found an effective and safe agent to prevent and treat bronchopulmonary dysplasia. Hydrocortisone is metabolised into phase I and phase II metabolites and phase II metabolites are prevalent over phase I metabolites. The pharmacokinetics of hydrocortisone have been studied in new-borns and infants and in children, infants and new-borns and the total body clearance is higher in children, infants, and new-borns than in new-borns and infants. The prophylaxis with hydrocortisone has been studied in infants and hydrocortisone prevents bronchopulmonary dysplasia and prophylactic hydrocortisone increases systolic blood pressure and improves oxygenation in infants. The treatment with hydrocortisone has been described in infants and children and hydrocortisone treats bronchopulmonary dysplasia and dermal application of hydrocortisone treats dermatitis. Hydrocortisone migrates into the breast milk in significant amounts. The aim of this study is to review the hydrocortisone dosing, pharmacokinetics, prophylaxis, and treatment in infants and children, and hydrocortisone metabolism and migration into the breast milk.

Keywords: *breast milk; children; dosing, efficacy-safety; hydrocortisone; infants; metabolism; pharmacokinetics; prophylaxis; treatment*

Structure-activity of corticoids

Chemical modifications of the cortisol molecule have generated derivatives with greater separation of glucocorticoid and mineralocorticoid activity; for a number of synthetic glucocorticoid, the effects on electrolytes are minimal even at highest doses used. In addition, these modifications have led to derivatives with greater potencies and with longer duration of action. A vast array of steroid preparations is available for oral, parenteral, and topical use. None of these currently available derivatives effectively separates anti-inflammatory effects from effects on carbohydrate, protein, and fat metabolism or from suppressive effects on the hypothalamic-pituitary-adrenal axis. Some steroids that are classified predominantly as glucocorticoids (e.g., cortisol) also possess modest but significant mineralocorticoid activity and thus may affect fluid and electrolyte handlings in the clinical setting. At doses used for replacement therapy in patients with primary adrenal insufficiency, the mineralocorticoid effects of these glucocorticoids are insufficient to replace that of aldosterone, and concurred therapy with a more potent mineralocorticoid generally is needed. In contrast, aldosterone is exceedingly potent with respect to Na+ retention but has only minimal effects on carbohydrate metabolism. Even at levels that maximally affect electrolyte balance, aldosterone has no significant glucocorticoid activity and thus acts as a pure mineralocorticoid [1].

Administration, distribution, metabolism and elimination of corticoids

Hydrocortisone and numerous congeners, including the synthetic analogues, are orally effective. Certain water-soluble esters of hydrocortisone and its synthetic congeners are administered intravenously to achieve high concentrations of drug rapidly in systemic or targeted body fluids. More prolonged effects are obtained by intramuscular injection of suspension of hydrocortisone, its esters, and congeners. Minor changes in chemical structure may markedly alter the rate of absorption time of onset of effect and duration of action. Glucocorticoids also are absorbed systemically from sites of local administration, such as synovial spaces, the conjunctival sac, skin, and respiratory tract. When administration is prolonged, when the site of application is covered with an occlusive dressing, or when large areas of skin are involved, absorption may be sufficient to cause systemic effects, including suppression of the hypothalamic-pituitary-adrenal axis. After absorption, 90% or more of cortisol in plasma is reversibly bound to protein under normal circumstances. In most tissues, only the fraction of corticosteroid that is unbound is active and can enter cells. Two plasma proteins account for almost all of the steroid-binding capacity; corticosteroid-binding globulin and albumin. Corticosteroid-binding globulin is an α globulin secreted by the liver that has high affinity for steroids (dissociation constant of about 1 nM) but relatively low total binding capacity, whereas albumin, also produced by the liver, has relatively large binding capacity but low affinity (estimated dissociation constant of 1 mM). In tissues with prolonged capillary transit time (e.g., liver, spleen), steroid dissociates from albumin. At high steroid concentrations, the capacity of corticosteroid-binding globulin binding is exceeded, and s slightly greater fraction of the steroid exists in the free state. Corticosteroid-binding globulin has relatively high affinity for cortisol and some of its synthetic congeners and low affinity for aldosterone and glucuronide-conjugated steroid metabolites; thus, greater percentages of these last steroids are found in the free form. A special state of physiological hypercortisolism occurs during pregnancy. The elevated circulating oestrogen levels include corticosteroid-binding globulin production and corticosteroid-binding globulin and total plasma cortisol increases several-folds; the physiological significance of these changes remains to be stablished. The aldosterone levels also ruse 3- to 10-fold in pregnancy, reflecting the activity of the elevated progesterone plasma levels as a mineralocorticoid receptor antagonist. Because progesterone is also a glucocorticoid receptor antagonist, it may contribute to the elevated levels of cortisol. As a general rule, the metabolism of steroid hormones involves sequential additions of O or

H atoms, followed by conjugation to form water-soluble derivatives. Reduction of the 4,5 double bond occurs at both hepatic and extra-hepatic sites, yielding inactive compounds. Subsequent reduction of the 3-ketone substituent to the 3-hydroxy group with sulfate or glucuronide by enzymatic reactions that take place in the liver and, to a lesser extent, in the kidney. Most of these A ring-reduced steroids are conjugated through the 3-hydroxy group with sulfate or glucuronide by enzymatic reactions that take place in the liver and, to a lesser extent in the kidney. The resultant sulfate esters and glucuronides are water soluble and are excreted in urine. Neither biliary nor faecal excretion is of quantitative importance in humans. Synthetic steroids with an 11-keto group such as cortisone and prednisone must be enzymatically reduced to the corresponding 11β-hydroxy derivative before they are biologically active. The type 1 isozyme of 11β-HSD (11β-HSD1) catalyses the reduction, predominantly in the liver but also in specialized sites as adipocytes, bone, eye, and skin. in settings in which this enzymatic activity is impaired, it is prudent to use steroids that do not require enzymatic activation (e.g., hydrocortisone or prednisolone rather than cortisone or prednisone). Such settings include individuals with severe hepatic failure and patients with the very rare conditions of cortisone reductase deficiency [1].

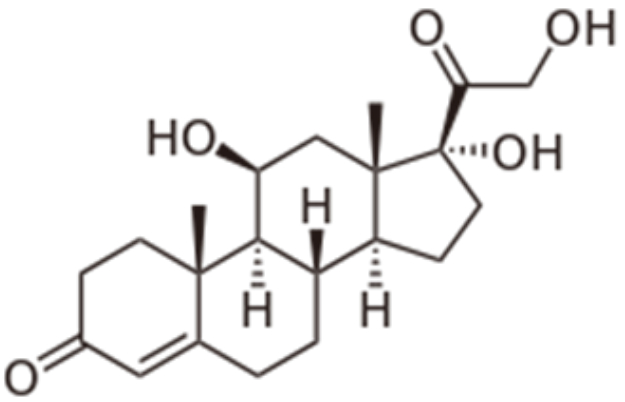

Figure 1: Hydrocortisone molecular structure (molecular weight = 362.46 grams/mole)

Clinical use of hydrocortisone in infants and children

Hydrocortisone has been used to manage congenital adrenal abnormality and adrenal insufficiency due to hypopituitarism. Hypotension in the preterm infant often responds to low-dose intravenous hydrocortisone [2]. Hydrocortisone is used to treat cortisol deficiency and pressor-resistant hypotension in infants and children. Adjuvant therapy with hydrocortisone is used to treat persistent hypoglycaemia. Hydrocortisone is the main adrenal corticosteroid with primarily glucocorticoid effects. Hydrocortisone increases the expression of adrenergic receptors in the vascular wall, thereby enhancing vascular reactivity to other vasoactive substances, such as norepinephrine and angiotensin II. Infants and children who are cortisol deficient (<15 µg/dl) likely respond to hydrocortisone and the blood pressure increases within 2 hours of the first dose. Hydrocortisone also stimulates the liver to form glucose from amino acids and glycerol and stimulates the deposition of glucose as glycogen. With hydrocortisone the peripheral glucose utilization is diminished, protein breakdown is decreased, and lipolysis is activated. The net result is an increase in blood glucose levels. The renal affects include increased calcium elimination. The elimination half-life of hydrocortisone is 9 hours in preterm infants. Hydrocortisone is incompatible with midazolam, nafcillin, pentobarbital, phenobarbital, and phenytoin [3] (Figure 1).

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "hydrocortisone dosing infants, children", "hydrocortisone efficacy, safety, infants, children", "hydrocortisone metabolism", "hydrocortisone pharmacokinetics infants, children", "hydrocortisone prophylaxis infants, children", "hydrocortisone treatment infants, children", and "hydrocortisone breast milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum, and The British National Formulary for Children [4] have been consulted.

Results

Administration schedules of hydrocortisone in infants and children

Administration to infants

Treatment of neonatal hypotension: Hydrocortisone often increases blood pressure as effectively as dopamine and may work when a catecholamine does not. Give: 2.5 mg/kg intravenously 4 times daily. This treatment is usually enough to reduce the need to use other vasopressor drugs. Try and withdraw treatment within 2 to 4 days, because steroid increases the risk of fungal infection, and also seems to increase the risk of focal gut perforation, especially in the infant is also given ibuprofen or indomethacin [2].

Prevention of bronchopulmonary dysplasia: Low-dose trials (0.5 mg/kg intravenously twice-daily for 12 days and half this for 3 days) delivered no benefit except to a subgroup with chorioamnionitis. Later development was not affected by such treatment. the results from different trials, however, are somewhat varied; the recently complete STOP-BRONCOPULMONARY DYSPLASIA study group examined the effects of hydrocortisone (or placebo) in very-low-birth-weight infants who were ventilated between 7 and 14 days of age. Whist they reported no statistical significantly differences in their primary outcome (a composite of death or bronchopulmonary at 36 weeks postmenstrual age) they did nonetheless have a significant difference in mortality-rate at that time that favoured treatment (15.5% versus 23.7%; odds ratio = 0.59 [95% confidence interval = 0.35 to 0.995]).

Treatment of bronchopulmonary dysplasia: Give: 2.5 mg/kg twice-daily for 7 days, and a reducing dose for further 2 weeks, was an effective as dexamethasone in one study, and did not appear to have the latter's detrimental effect on development.

Treatment of congenital adrenal hyperplasia: Give: 3 to 5 mg/m^2 of hydrocortisone thrice-daily, plus at least 200 µg of fludrocortisone once-daily, provide a good starting point for neonatal care. Infants with 21-hydrolase deficiency usually need an additional 2 to 4 mmol/kg of sodium daily.

Treatment of adrenal hypoplasia: Production of cortisol normally averages to 6 to 9 mg/m^2 daily and, making allowance for absorption, 8 to 10 mg/m^2 of hydrocortisone daily in 3 divided doses given orally will meet normal replacement needs (although need may rise several-fold during any acute illness). Give a higher dose in the morning than at other times.

Treatment of Addisonian crisis: This requires intravenous glucose and 10 mg bolus followed by a continuing 100 mg/m^2 daily by infusion of hydrocortisone. Rapid fluid replacement may be necessary with 0.9% sodium chloride. The high serum potassium almost always correct itself, but 2 ml/kg of 10% calcium gluconate and/or an infusion of glucose and insulin may be needed if a cardiac arrhythmia develops. In infants, aged 1 to 12 months, give glucose intravenously and an mg/m^2 initial dose of 2 to 4 mg/kg slow intravenous bolus injection then 2 to 4 mg/kg 4 times daily.

Administration to children

Intravenous administration of hydrocortisone for treatment of acute adrenocortical insufficiency (Addison crisis) [4].

Children aged 1 month to 11 years: Give initially 2 to 4 mg/kg of hydrocortisone, and then 2 to 4 mg/kg 4 times-daily, adjust the dose according to the response, when stable reduce the dose over 4 to 5 days to oral maintenance dose.

Children aged 12 to 17 years: Give: 100 mg of hydrocortisone 4 times-daily or thrice-daily.

Oral treatment of congenital adrenal hyperplasia

Children: Give: 9 to 15 mg/m^2 of hydrocortisone in 3 divided doses, and then adjust the dose according to the response.

Oral treatment of (1) adrenal hypoplasia, (2) Addison disease, (3) chronic maintenance or (4) replacement therapy

Children: Give: 8 to 10 mg/m^2 daily of hydrocortisone daily in 3 divided doses, the larger dose to be given in the morning and the smaller dose in the evening, higher doses may be needed.

Intravenous treatment of inflammatory bowel disease-induction of remission

Children aged 2 to 17 years: Give: 2.5 mg/kg of hydrocortisone 4 times-daily (maximum per dose = 100 mg).

Continuous intravenous infusion of inflammatory bowel disease-induction of remission

Children aged 2 to 17 years: Give: 10 mg/kg of hydrocortisone daily (maximum = 400 mg daily).

Rectal treatment of (1) ulcerative colitis and (2) proctosigmoiditis

Children aged 2 to 17 years: Give initially 1 metered application of cortisone 1 to 2 times-daily for 2 to 3 weeks, and then reduce the dose to 1 metered application once-daily on alternative days, to be inserted in the rectum.

Intravenous treatment of (1) acute hypersensitivity reactions and (2) angioedema

Children aged 1 to 5 months: Give initially 25 mg of hydrocortisone thrice daily, and then adjust the dose according to the response.

Children aged 6 months to 5 years: Give initially 50 mg of hydrocortisone thrice daily, and then adjust the dose according to the response.

Children aged 6 to 11 years: Give initially 100 mg of hydrocortisone thrice daily, and then adjust the dose according to the response.

Children aged 12 to 17 years: Give initially 200 mg of hydrocortisone thrice daily, and then adjust the dose according to the response.

Intravenous treatment of hypotension resistant to inotropic treatment and volume replacement (limited evidence)

Children: Give: 1 mg/kg of hydrocortisone thrice-daily (maximum per dose = 100 mg).

Intravenous treatment of (1) severe acute asthma and (2) life-threatening acute asthma

Children aged 1 month to 1 year: Give: 4 mg/kg of hydrocortisone 4 times-daily (maximum per dose = 100 mg), alternatively 50 mg 4 times-daily until conversion to oral prednisolone is possible, the dose given preferentially, as sodium succinate.

Children aged 5 to 11 years: Give: 4 mg/kg of hydrocortisone 4 times-daily (maximum per dose = 100 mg), alternatively 100 mg 4 times-daily until conversion to oral prednisolone is possible, the dose given, preferentially, as sodium succinate.

Children aged 12 to 17 years: Give: 4 mg/kg of hydrocortisone 4 times-daily (maximum per dose = 100 mg), alternatively 100 mg 4 tomes-daily until conversion to oral prednisolone is possible, the dose, preferentially, as sodium succinate.

Efficacy and safety of hydrocortisone in infants and children

Early treatment with low-dose hydrocortisone effectively and safely prevents bronchopulmonary dysplasia or death in preterm infants exposed to chorioamnionitis [5]. Hydrocortisone efficaciously and safely treats hypotension associated with impaired adrenal function among critically ill newborns [6]. Early systemic hydrocortisone is an effective therapy for the prevention of bronchopulmonary dysplasia in preterm infants [7]. Hydrocortisone is efficacy, safe, and easy to administer to newborns, infants, and children and is it rapidly absorbed [8]. Hydrocortisone is an effective and appropriate treatment for diaper dermatitis in infants and children [9]. Hydrocortisone normalizes the cardiovascular status and decreases pressor requirement in preterm infants [10]. Hydrocortisone effectively and safely treats hypotension in children undergoing cardiac surgery [11]. Hydrocortisone butyrate 0.1% in lipocream effectively and safely treats dermatitis in a paediatric population [12].

Metabolism of hydrocortisone

Sarkar *et al.* [13] studied the metabolism of hydrocortisone using human liver perfusion. Phase I metabolites include tetrahydrocortisone and dihydrocortisol which accounted to 8 to 10% of the total metabolites, and phase II metabolites are tetrahydrocortisol and tetrahydrocortisone glucuronides and hydrocortisone sulfate which accounts to 45 to 52% of total metabolites (Figures 2-4).

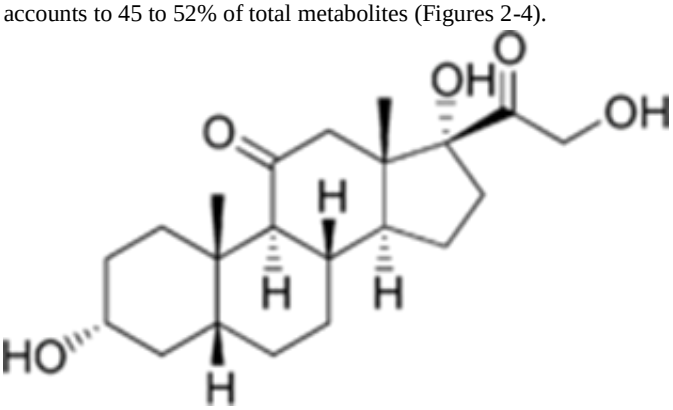

Figure 2: Tetrahydrocortisone molecular structure (molecular weight = 364.4758 grams/mole)

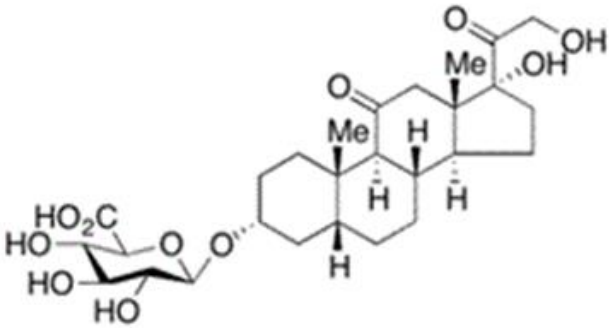

Figure 3: Tetrahydrocortisone 3-glucuronide molecular structure (molecular weight = 540.606 grams/mole)

Bailey *et al.* [14] investigated the metabolism of hydrocortisone in human liver microsomes and the metabolites which are formed are cortisone, dihydrocortisol, dihydrocortisone and 6β-hydroxycortisol (Figures 5-7).

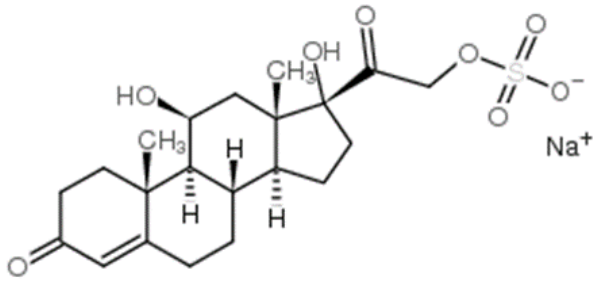

Figure 4: Hydrocortisone sulfate molecular structure (molecular weight = 464.505 grams/mole)

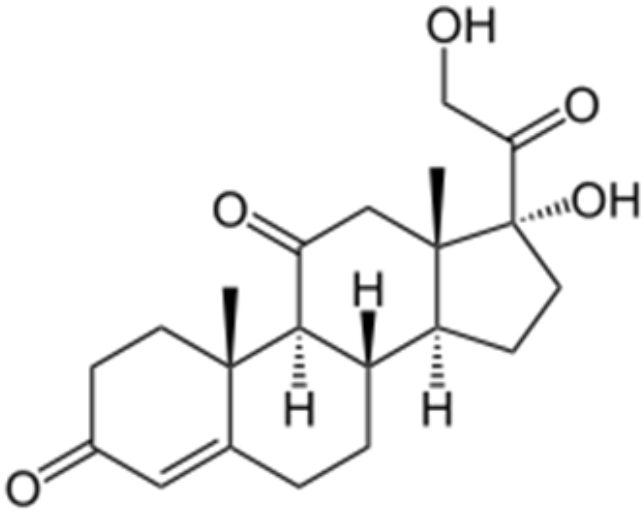

Figure 5: Cortisone molecular structure (molecular weight = 360.4 grams/mole)

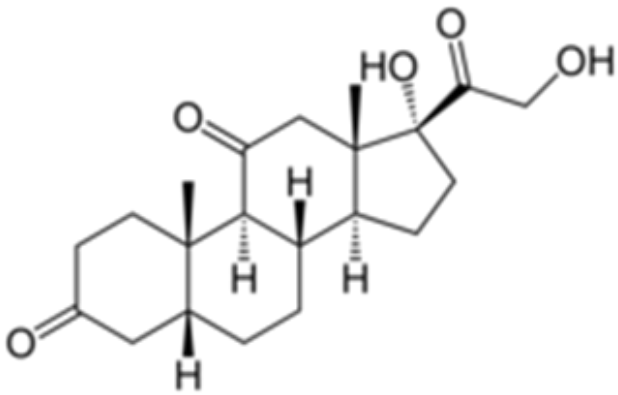

Figure 6: Dihydrocortisone molecular structure (molecular weight = 362.46 grams/mole)

Pharmacokinetics of hydrocortisone in newborns and infants

Vezina *et al*. [15] studied the pharmacokinetics of hydrocortisone in 62 newborns and infants with median postmenstrual, postnatal ages, and body weight of 28 weeks (range, 28 to 41), 0.7 weeks (range, 0.1 to 9.3), and 1.2 kg (range, 0.5 to 4.4). Thirty-three (53.2%) subjects were males and 29 (46.8%) were females and hydrocortisone were intravenously infused at a dose of 45 mg/m^2 daily divided in 4 doses.

This table shows that the distribution volume of unbound hydrocortisone is larger than the water volume. The most important biological covariates for predicting the total body clearance and the distribution volume of unbound hydrocortisone are the body weight and the postmenstrual age, and there is a remarkable variability of the

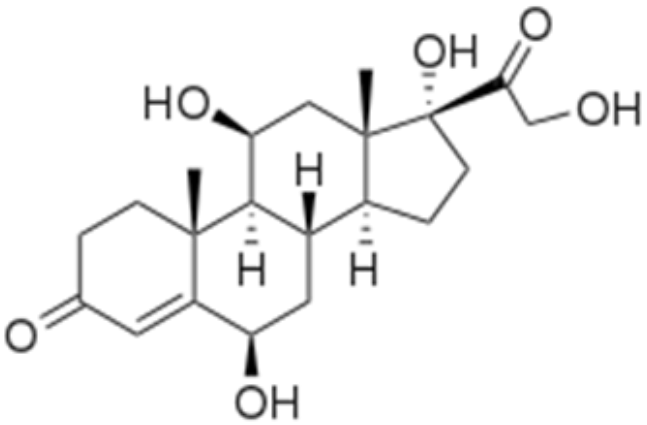

Figure 7: 6β-Hydroxycortisol molecular structure (molecular weight = 378.46 grams/mole)

pharmacokinetic parameters. This variability may be accounted by the wide variability of demographic characteristics of the subjects included in the study and by their diseases.

Pharmacokinetics of hydrocortisone in children, infants, and newborns

Michelet *et al.* [16] investigated the pharmacokinetics of hydrocortisone in 12 children aged 39.9 months (range, 24.8 to 59.6) with a body-weight of 16.2 kg (range, 12.2 to 21.0), in 6 infants aged 16.6 months (range, 4.1 to 22.1) with a body-weight of 11.1 kg (range, 6.7 to 12.5), and in 6 newborns aged 0.77 months (range, 0.53 to 0.87) with a body-weight of 3.65 kg (range, 2.80 to 4.90). Twenty-three subjects had congenital adrenal hyperplasia and 1 subject had hypopituitarism and hydrocortisone was administered orally at a dose of 2.5 mg (range, 2.0 to 4.0) to children, at a dose of 2.0 mg (range, 2.0 to 2.5) to infants, and at a dose of 0.5 mg (range, 0.4 to 0.7) to newborns (Table 2).

Table 2: Pharmacokinetic parameters of hydrocortisone which are obtained in 12 children, 6 infants and 6 newborns, by Michelet *et al.* [16]

Disposition model	Parameter estimate	Bootstrap median (95% CI)	LLP (95% CI)
Maximum absorption rate (nmol)	4,810 (19%)	5,053 (2,880 – 7,530)	3,589 – 8,550
Vmabs (nmol/h)	21,600 (10%)	21,900 (17,600 – 26,500)	18,500 (18,500 – 26,000)
TBC/F (L/h)	400 (7%)	412 (353 – 468)	255 – 473
DVo/F (L)	10.6 (11%)	10.6 (8.58 – 12.6)	9.31 – 12.0
Q/F (L/h)	160 (18%)	159 (104 – 237)	123 – 210
DVp/F (L)	124 (14%)	124 (84.6 – 163)	102 – 150)
BASE (nM)	13.3 (6%)	13.3 (12.7 – 13.8)	11.8 – 15.0
Interindividual variability			
ωKabs (CV%)	48.1% (35%)	45.5% (30.2 – 62.5)	14.1 – 81.8
ωVabs (CV%)	46.0% (17%)	45.5% (30.2 – 62.6)	35.1 – 61.8
ωTBC (CV%)	19.3 (17%)	18.4 (10.6 – 26.2)	13.5 – 26.5
ωBASE (CV%)	34.4% (22)	32.9% (20.0 – 48.0)	26.3 – 47.2
ωF (CV%)	36.0% (22%)	535.1 % (18.3 – 51.6)	25.9 – 49.3
Residual variability			
oexpb (CV%)	14.5% (8%)	14.4% (12.5 – 16.9)	14.0 – 15.1

TBC: Total Body Clearance, F: Bioavailability, LLP: Log-Likelihood Profiling, Vmabs: Maximum Absorption Rate, DVo/F: Apparent Central Distribution Volume, Q/F: Apparent Intercompartmental Total Body Clearance, DVp/F: Apparent Peripheral Distribution Volume, BASE: Cortisol Baseline of Dexamethasone Suppressed Healthy Adults, ω: Interindividual Variability, Kabs: Absorption Rate, Vabs: Distribution Volume, oexpb: Residual Variability

This table shows that hydrocortisone is rabidly absorbed following oral dosing, the central distribution volume is larger than the water volume, the central distribution volume is smaller than the peripheral distribution volume, and there is a remarkable

interindividual variability in the pharmacokinetic parameters. This variability may be accounted by the wide variability of the demographic characteristics of the subjects included in the study and by their diseases. The study carried out by Michelet *et al.* [16] shows that newborns have a lower and more variable total body clearance than infants and children, which can potentially be explained by the lower metabolism of hydrocortisone and a lower elimination-rate. The total body clearance is greater in children than in infants and the central distribution volume is smaller in children that in infants. For comparison of the total body clearance and the distribution volume obtained in infants see (Table 1). Hydrocortisone is cleared from the body by metabolism and renal route and both elimination pathways increase with infant maturation and child development. Hydrocortisone is extensively bound to plasma protein and the plasma protein concentration is lower in newborns and infants than in children, infants and newborns and such a difference may explain the larger distribution volume observed in newborns and infants than in children, infants, and newborns.

Table 1: Pharmacokinetic parameter estimates of unbound hydrocortisone which are obtained in 62 newborns and infants, by Vezina *et al.* [15]

Parameter	Final estimate	%RSE	95% CI	Bootstrap (median)	Bootstrap 95% CI
TBC (L/h)	20.2	10.8	15.9 – 24.5	20.4	16.1 – 25.6
PMA effect	0.11	17.6	0.075 – 0.145	0.11	0.076 – 0.154
DV (L)	244	21.5	160 – 328	270	170 – 592
Baseline cortisol (ng/ml)	1.37	16.1	0.792 – 1.95	1.39	0.882 – 2.04
Variability for TBC (CV%)	0.293 (54.1%)	22.6	0.163 – 0.423	0.293	0.157 – 0.484
Variability of cortisol (CV%)	2.41 (155%)	11.9	1.85 – 2.97	2.37	1.78 – 2.90
Variability for RV proportional error model (CV%)	0.328 (57.3%)	13.2	0.243 – 0.413	0.326	0.246 – 0.413
RV by additive error model $\pm$ SD	0.049 $\pm$ 0.220	15.8	0.034 – 0.064	0.048	0.033 – 0.065

TBC: Total Body Clearance, PMA: Postmenstrual Age, DV: Distribution Volume, %RSE: 100%*Standard Error Estimate, CI: Confidence Interval., VR: Residual Variability, CV: Coefficient of Variance, SD: Standard Deviation

Prophylaxis with hydrocortisone in infants

Early low-dose hydrocortisone prevents bronchopulmonary dysplasia in preterm infants [17]. Prophylactic hydrocortisone increases the survival-rate in preterm infants with bronchopulmonary dysplasia [18]. Prophylaxis with hydrocortisone significantly decreases the mortality-rate and improves the survival-rate in infants with bronchopulmonary dysplasia [19]. Prophylactic hydrocortisone increases systolic blood pressure and improves oxygenation in infants with persistent pulmonary hypertension [20]. Early prophylaxis with low-dose hydrocortisone treats adrenal insufficiency in preterm infants [21]. A prophylactic dose of hydrocortisone effectively treats refractory hypotension in preterm infants [22].

Treatment of infants and children with hydrocortisone

Early low-dose hydrocortisone therapy increases the survival-rate in preterm infants with bronchopulmonary dysplasia [23]. Early low-dose hydrocortisone confers benefits in preterm infants with bronchopulmonary dysplasia [24]. Early low-dose hydrocortisone successfully treats bronchopulmonary dysplasia in preterm infants [25]. Early low-dose hydrocortisone reduces moderate or severe bronchopulmonary dysplasia in preterm infants [26]. Administration of postnatal hydrocortisone treats bronchopulmonary dysplasia in preterm infants [27]. Early low-dose of hydrocortisone treats bronchopulmonary dysplasia and does not induce adverse-effects in children [28]. Hydrocortisone should replace dexamethasone in the treatment of infants with chronic lung disease [29]. Neonatal hydrocortisone treats bronchopulmonary dysplasia and has no long-term effects on neurodevelopment in children [30]. Perinatal hydrocortisone has no long-term effects on either neuro-structural brain development and neurocognitive outcomes in children [31]. Hydrocortisone 0.1% lotion effectively and safely treats mild to moderate atopic dermatitis in children aged 3 months to 18 years [32]. Hydrocortisone ointment is a valuable treatment of eczema in infants and children [33].

Migration of hydrocortisone into the breast milk

The concentration of hydrocortisone was measured in the breast-milk obtained from 23 lactating women and it averages to 1.6 ng/ml over 24 hours. The concentrations of hydrocortisone in the breast-milk are higher in the morning than in the evening [34]. Hydrocortisone was measured in the breast-milk of 13 lactating women and the concentration of hydrocortisone in the breast-milk ranges from 1.45 to 8.34 ng/ml [35]. The concentrations of hydrocortisone were measured in the breast-milk obtained from 7 women who delivered spontaneously and in 6 women who underwent elective Caesarean section. In the women with spontaneous delivery, the breast-milk concentrations of hydrocortisone is 17.2, 16.8, and 7.4 ng/ml on days 1, 2, and 3, respectively, after delivery. In the women who underwent Caesarean section, the breast-milk concentrations of hydrocortisone are 26.5, 15.1, and 14.1 ng/ml on days 3, 4 and 6, respectively, after delivery [36]. Hydrocortisone concentrations were measured in the breast-milk of 11 lactating women monthly up to 12 months. The breast-milk concentrations of hydrocortisone, between months 2 and 12 postpartum, average to 7.2 ng/ml but it varied with time and among individuals and ranges from 0.2 to 32 ng/ml [37].

Discussion

Hydrocortisone may be administered intravenously, orally, or topically and following oral and topical administration hydrocortisone is well absorbed. In infants, hydrocortisone has been used to treat hypotension, to prevent and treat bronchopulmonary dysplasia, to treat congenital adrenal hypoplasia, and Addisonian crisis [2]. In children, hydrocortisone has been used to treat acute adrenocortical insufficiency (Addison crisis), congenital adrenal hyperplasia, inflammatory bowel disease, ulcerative colitis, proctosigmoiditis, acute hypersensitivity reactions, angioedema, hypotension, severe acute asthma, and life-threatening acute asthma [4]. Hydrocortisone has been found efficacy and safe in infants and children [5-12]. Early treatment with low-dose hydrocortisone prevents bronchopulmonary dysplasia in preterm infants exposed to chorioamnionitis [5], hydrocortisone effectively and safely treats hypotension associated with impaired adrenal function in critically ill newborns [6], early systemic hydrocortisone prevents bronchopulmonary dysplasia in preterm infants [7], hydrocortisone is efficacy, safe, and easy to administer to newborns, infants, and children and is rapidly absorbed [8], hydrocortisone effectively treats diaper dermatitis in infants and children [9], hydrocortisone normalizes cardiovascular status and decreases the blood pressor requirement in preterm infants [10], hydrocortisone effectively and safely treats hypotension in children undergoing cardiac surgery [11], and hydrocortisone butyrate 0.1% in lipocream effectively and safely treats dermatitis in a paediatric population [12]. The metabolism of hydrocortisone has been studied

using human liver perfusion. Phase I metabolites are tetrahydrocortisone and dihydrocortisol which account to 8 to 10% of the total metabolites and phase II metabolites are tetrahydrocortisol and tetrahydrocortisone glucuronides and hydrocortisone sulfate which account to 45 to 52% of the total metabolites [13]. The metabolism of hydrocortisone has been studied in human liver microsomes and the metabolites generated are cortisone, dihydrocortisol, dihydrocortisone, and 6β-hydroxycortisol [14]. The pharmacokinetics of hydrocortisone have been studied in newborns and infants and the total body clearance of hydrocortisone is 20.2 L/h [15]. The pharmacokinetics of hydrocortisone have been studied in children, infants and newborns and the total body clearance of hydrocortisone is 400 L/h [16]. Hydrocortisone is cleared from the body by metabolism and renal route and both elimination pathways increase with infant maturation and child development. This consideration explains the higher total body clearance obtained in children, infants, and newborns than that obtained in newborns and infants. The prophylaxis with hydrocortisone has been conducted in infants [17-22]. Early low-dose of hydrocortisone prevents bronchopulmonary dysplasia in preterm infants [17], and prophylactic hydrocortisone increases the survival-rate in preterm infants with bronchopulmonary dysplasia [18], prophylactic hydrocortisone decreases the mortality-rate and improves the survival-rate in preterm infants with bronchopulmonary dysplasia [19], and prophylactic hydrocortisone increases systolic blood pressure and improves oxygenation in infants with bronchopulmonary dysplasia [20]. Early prophylaxis with low-dose hydrocortisone treats adrenal insufficiency in preterm infants [21], and prophylactic hydrocortisone treats refractory hypotension in preterm infants [22]. The treatment of infants and children with hydrocortisone has been extensively studied [23-33]. Early low-dose hydrocortisone treats bronchopulmonary dysplasia in preterm infants [23-27]. Early low-dose hydrocortisone treats bronchopulmonary dysplasia and does not induce adverse-effects in children [28]. Hydrocortisone should replace dexamethasone in the treatment of infants with chronic lung disease [29]. Neonatal hydrocortisone treats bronchopulmonary dysplasia without inducing long-term effects on neurodevelopment in children [30]. Perinatal hydrocortisone has no long-term effects on either neuro-structural brain development and neurocognitive outcomes in children [31]. Hydrocortisone ointment treats atopic dermatitis [32] and eczema [33] in infants and children. Hydrocortisone migrates into the breast-milk in significant amounts [34-37].

In conclusion, hydrocortisone may be administered intravenously, orally, or topically and after oral and topic administration hydrocortisone is well absorbed. In infants, hydrocortisone has been used to treat hypotension, to prevent and treat bronchopulmonary dysplasia, to treat congenital adrenal hypertension, to treat adrenal hypoplasia, and to treat Addisonian crisis. In children, hydrocortisone is used to treat adrenocortical insufficiency (Addison crisis), to treat congenital adrenal hyperplasia, adrenal hypoplasia, inflammatory bowel disease, ulcerative colitis, proctosigmoiditis, acute hypersensitivity reactions, angioedema, resistant hypotension, severe acute asthma, and life-threatening acute asthma. The efficacy and safety of hydrocortisone have been described in infants and children. Hydrocortisone is extensively metabolised into phase I and phase II metabolites and the latter metabolites are prevalent over the former metabolites. The pharmacokinetics of hydrocortisone have been studied in newborns and infants and in children, infants and newborns and the total body clearance is higher in children, infants, and newborns that in newborns and infants. The prophylaxis and treatment with hydrocortisone have been reported in infants and children and hydrocortisone migrates into the breast-milk in significant amounts. The aim of this study is to review the clinical pharmacology of hydrocortisone 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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