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The Effect of Glucocorticoid Therapy on Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression in Pediatrics: A Literature Review

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ABSTRACT

Corticosteroids are a class of steroid hormones, a hormone produced by the adrenal gland in response to the adrenocorticotropic hormone (ACTH) released by the pituitary gland. The glucocorticoid (GC) group is a corticosteroid whose main effects on metabolism and anti-inflammatory, whereas its effect on water balance and electrolytes is small or insignificant. GC are standard therapy to reduce inflammation and activation of the immune system in various diseases, this is why these drugs are widely used for various diseases. The side effects of GC involve most major organ systems such as musculoskeletal, gastrointestinal, cardiovascular, endocrine, neuropsychiatric, dermatological, ocular, and immunologic. HPA axis suppression occurs due to endogenous and exogenous glucocorticoids do negative feedback control that is short-loop feedback and long-loop feedback on the HPA axis by suppressing hypothalamic corticotropin-releasing hormone (CRH) production and ACTH secretion. It is characterized by the decrease of ACTH levels with clinical manifestation hypotension, hypoglycemia, weakness/fatigue, nausea, vomiting and can lead to an adrenal crisis. Complication of GC therapy increased, in proportion to dose, type/strengthness GC, duration of therapy and increased frequency of administration. This article attempts to review the effect of glucocorticoid on HPA axis supression in pediatrics based on literature review.

Keywords: Glucocorticoid; HPA axis suppression; Adrenal suppression; Paediatrics

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INTRODUCTION

Corticosteroid drugs are widely used in the medical field, and also in many pediatric cases [1]. Corticosteroid is a class of steroid hormone, which is produced by adrenal glands as a response to adrenocorticotropic hormone (ACTH) released by pituitary gland [2]. These hormones play a role in many physiological systems of the body, such as in the response towards stress, immunity system, inflammatory regulation, carbohydrate metabolism, protein breakdown, blood electrolyte levels, and behaviors [3].

Glucocorticoids are a form of corticosteroid which has a major effect towards metabolism and substantial anti-inflammatory properties, while its influence towards water and electrolyte balance is negligible [4,5]. Glucocorticoids are a standard therapy in reducing inflammation and immune system activation in various diseases. This is the reason why this drug is commonly used in the treatment for various diseases, and even frequently called the "life-saving drug", yet it may also cause adverse reactions [6]. Synthetic GC is available in different formulations (oral, intravenous or intramuscular, inhalation and topical) [5].

Main side effects of glucocorticoid involve most of main organ systems such as musculoskeletal, gastrointestinal, cardiovascular, endocrine, neuropsychiatric, dermatologic, ocular, and immune system [6,7]. Complications of systemic glucocorticoid therapy increase proportional to increase in dose, duration of therapy, and frequency of administration [7,8].

Exogenous glucocorticoid administration may suppress hypothalamic-pituitary-adrenal (HPA) axis and has been shown to suppress adrenal gland during long-term administration with a significantly variable individual response. Supraphysiologic dosage of GC will inhibit corticotropin-releasing hormone (CRH) production and ACTH release [5,6].

Clinical manifestations of suppressed HPA axis vary greatly, shown by several presenting symptoms such as fatigue, malaise, nausea, vomiting, diarrhea, abdominal pain, growth delay, and weight loss in children. Children can also experience hypotension, shock, decrease of consciousness, lethargy, hypoglycemia, seizure, and even death [9,10]. Moreover, an adrenal crisis can occur, which is categorized as a medical emergency with non-specific manifestations such as severe lethargy, hypoglycemia, hypotension, decreased/altered consciousness, severe vomiting and diarrhea, and can be fatal [1,11]. Suppression of endogenous ACTH can cause adrenocortical hypoplasia or atrophy [5].

The duration of HPA axis suppression after the discontinuation of glucocorticoid in children shows no clear pattern. Recovery time of adrenal glands can be short (several days), several weeks or even up to 1 year after glucocorticoid discontinuation, in which this depends on the duration and dose of corticosteroid and the speed of tapering [6,12,13].

PHYSIOLOGY OF NORMAL HPA AXIS PATHWAY AND CLINICAL APPLICATION OF GLUCOCORTICOID IN PEDIATRICS

Cortisol is an endogenous glucocorticoid in human produced by adrenal glands. Glucocorticoid secretion is determined by the fluctuation of ACTH release by pituitary which is regulated by corticotrophin releasing hormone (CRH) and arginine vasopressin (VAP), which are peptide hormones secreted by hypothalamus. The three organs (i.e. hypothalamus, pituitary, and adrenal glands) are collectively called as hypothalamic-pituitary-adrenal (HPA) axis, a system which maintains the glucocorticoid level in the body. HPA axis has typical a diurnal pattern of regulation, negative feedback regulation by adrenal corticosteroid, and increased steroidogenesis as a response against stress [1,13,14].

If the system produces too much ACTH, causing an excess of cortisol, then the cortisol will gives feedback and inhibits CRH production by hypothalamus and decrease the sensitivity of cells producing ACTH towards CRH by directly acting in the anterior hypophysis. Through these double approaches; cortisol controls negative feedback to stabilize its own concentration in the plasma. If cortisol level starts to drop, inhibitory effect of cortisol towards the hypothalamus and anterior hypophysis will decrease, thus increasing the factors which stimulate secretion of cortisol (CRH-ACTH) (Figure 1) [1,13].

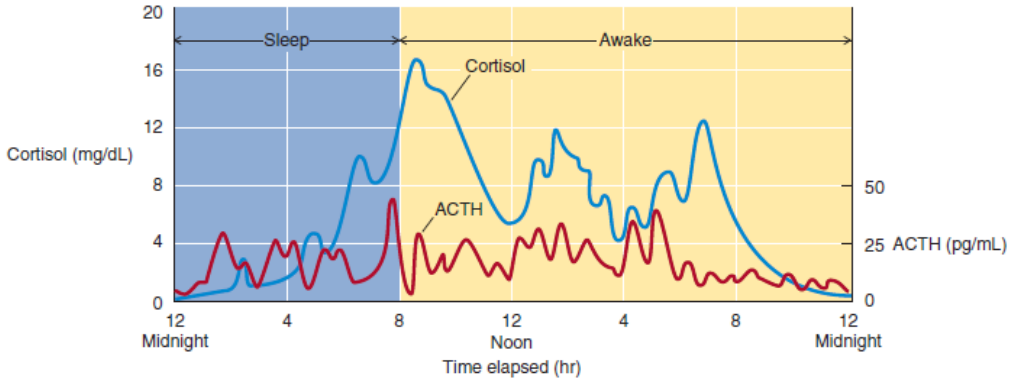

Figure 1. The physiological rhythm of cortisol secretion in the body [16]

Physiological secretion of ACTH follows circadian and ultradian rhythm through the control of suprachiasmatic nucleus (SCN) of the anterior hypothalamus by utilizing CRH hormone complex [15]. CRH will stimulate ACTH and release cortisol in a pulsating manner in which the cortisol level between 11 pm to 1 am will be very low or undetected. Afterwards, the cortisol level increased and peaked in the early hours of morning (between 6 am to 9 am), and gradually decreased throughout the day. There is no difference in physiological cortisol secretion in relation to body weight or gender (Table 1) [5,16].

Table 1. Normal range of ACTH and cortisol in pediatrics [17]

Test	Condition	Conventional Units	Conversion Factor	SI Unit
ACTH	<3 y	Not established		
	3-17 y	9-57 ng/L	0,222	2-12.7 pmol/L
Cortisol Serum	Premature (31-35 wk)	<15 µg/dl	27,59	<414 nmol/L
	Term Infants (3 d)	<14 µg/dl		<386 nmol/L
	1-17 y	2-17 µg/dl		55-469 nmol/L

Overall, glucocorticoids are used as:

a. Replacement therapy. It is given to patients with both acute and chronic adrenal insufficiency, be it secondary or primary [18]. In developed countries, primary adrenal insufficiency is most commonly caused by autoimmune adrenal diseases, while adrenalitis TB is the most common etiology in developing countries [14].

b. As the suppressor of androgen secretion in congenital adrenal hyperplasia (CAH) [18].

As the therapy for non-endocrine disorders (kidney diseases, infection, transplantation reaction, rheumatic diseases, allergy, etc.) due to the immunosuppressive and anti-inflammatory properties it possessed [18,19].

PATOPHYSIOLOGYOF HPA AXIS SUPPRESSION

Exogenous glucocorticoid (GC) therapy may cause HPA axis suppression by reducing CRH synthesis and secretion and inhibiting ACTH release from anterior hypophysis. In long-loop negative feedback, ACTH binded with Melanocortin 2 receptor (MC2R) will be reduced and caused decreased activation of protein G. As a result, the productions of adenylyl cyclase and cyclic adenosine monophosphate (cAMP) are also decreasing. This causes the decrease in Protein Kinase A (PKA) stimulation which causes a decrease in cortisol secretion [1,16,18].

In short loop negative feedback, exogenous glucocorticoid can suppress CRH secretion from hypothalamus, and there is a subsequent decrease in the binding of CRH with G protein-coupled receptor (GPCR) on corticotrophin cell membrane in the anterior hypophysis. Decrease in protein G activation which stimulates adenylyl cyclase will

reduce cAMP production. This will cause the decrease of PKA stimulation which activates L-type Ca2+ channels, thus decreasing Ca2+ concentration and reducing ACTH release. On the long term, decreased activity of CRH receptor will cause reduced gen transcription and proopiomelanocortin (POMC) synthesis which will reduce ACTH synthesis. Overtime, this can cause adrenal atrophy (Figure 2) [1,16,18].

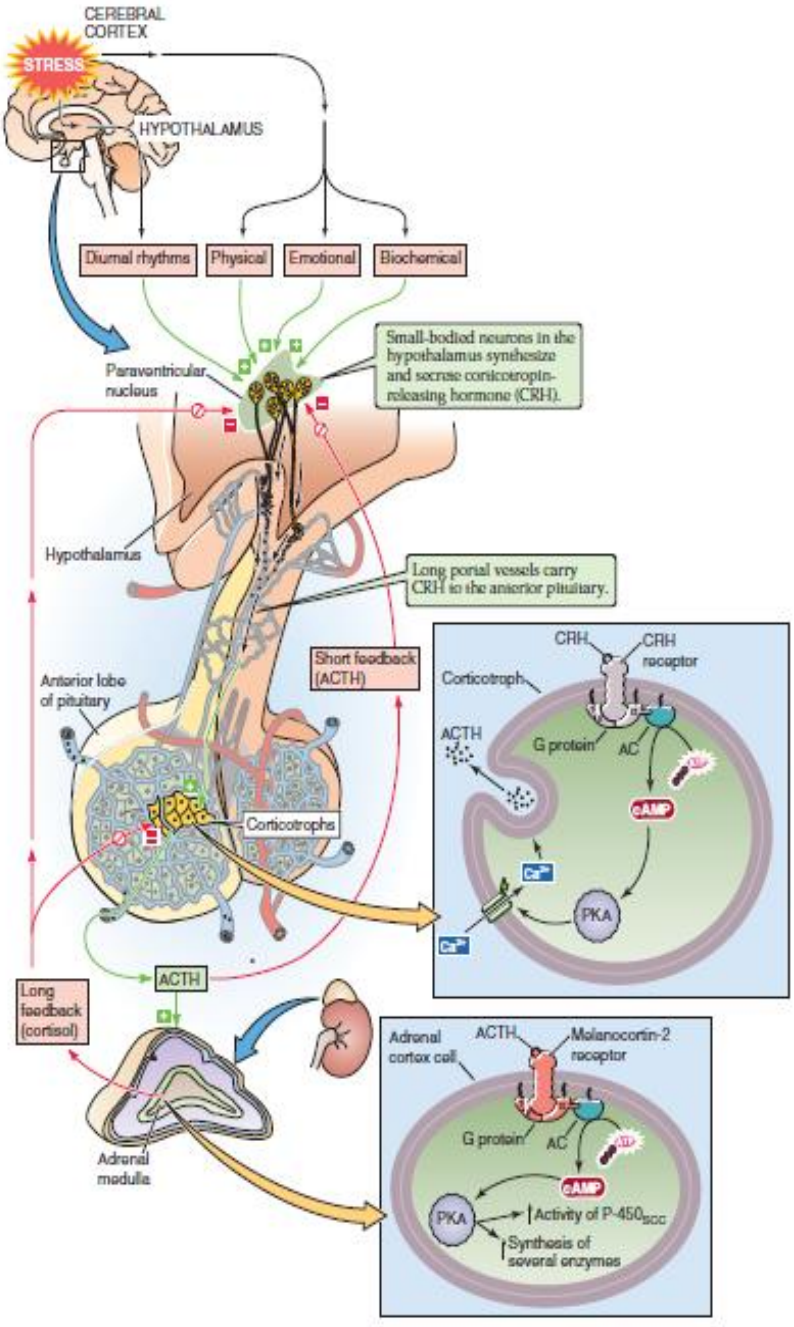

Figure 2. Negative feedback mechanism of glucocorticoid administration [16]

Glucocorticoid effect can be divided into acute and delayed phase. Acute phase usually happens within minutes after administration, which is associated with increased cortisol level and inhibition of ACTH and CRF release. Delayed

phase occurs after 2-20 hours and continues until a couple of days. This phase is mainly related to gen transcription factor inhibition from by pro-opiomelanocortin (POMC), causing decrease of ACTH synthesis [3].

The required dose to cause HPA axis suppression depends on: (a) time of steroid administration: morning dose yields less suppression; (b) steroid preparation: long acting preparations yields more suppression; (c) duration of therapy (d) route of administration: parenteral route's suppression is greater than the oral or topical route, but suppression through inhalation route is also frequently reported [20].

There are several tests that can be used for evaluation of HPA axis suppression, such as the high dose ACTH stimulation test (HDST) and the low dose ACTH stimulation test (LDST). HDST (250 μg) uses supra-physiological doses of ACTH to stimulate the atrophic adrenal glands, resulting in false-negative results. LDST is also used for assessment of the HPA axis after prolonged use of GC drugs. Corticotrophin Releasing Hormone (CRH) tests can also be used in patients taking GC treatment for a long time, as it can assess both the ACTH response and cortisol and can distinguish secondary and tertiary adrenal insufficiency [3,18]. Adrenal suppression was defined as a first morning cortisol level <108 nmol/L or an abnormal LDST (cortisol peak <500 nmol/L) [21].

CLINICAL MANIFESTATION OF HPA AXIS SUPPRESSION

Patients with adrenal suppression may appear well if minimum GC level is supported with exogenous GC. However, in several cases, the support is inadequate and symptoms of adrenal insufficiency occur. Subsequently, with the presence of adrenal atrophy, sudden discontinuation of GC therapy or addition of acute stressor will cause symptom of adrenal insufficiency and can potentially result in adrenal crisis [1,3].

Adrenal suppression has potentially life-threatening consequences, signs and symptoms can be harmful and non-specific, including fatigue, nausea/vomiting/diarrhea /abdominal pain, muscle weakness, weight loss, hypoglycemia and mood changes. Adrenal crisis is a medical emergency which can present with non-specific manifestations such as severe lethargy, hypoglycemia, hypotension, decreased/altered consciousness, seizure, fever, severe vomiting and diarrhea and can be fatal [1,11].

CLINICAL TRIALS REGARDING THE EFFECT OF GLUCOCORTICOIDS ON HYPOTHALAMUS–PITUITARY–ADRENAL AXIS OFPEDIATRICS POPULATION

Systemic Glucocorticoid

A systematic review analyzed the effect of short course oral corticosteroid (≤ 14 days) in children towards the occurrence of adverse drug reactions (ADR). The three most common ADR were vomiting, changes in behavior, and sleep disturbance, with the incidence rate of 5.4%, 4.7%, and 4.3%, respectively. Meanwhile HPA axis suppression was detected in 43 out of 53 patients [8].

Glucocorticoid is commonly used in the treatment of acute lymphoblastic leukemia (ALL) in children due to its lympholytic effect [18]. In two meta-analyses with the total of 298 and 218 children with ALL, adrenal function examinations were performed. Adrenal insufficiency occurred in almost all of the children during the first days after discontinuation of glucocorticoid treatment. Most of the cases resolved within several weeks, but few children suffered from continuous lack of adrenaline which lasts as long as 34 weeks. There were no difference in incidence and duration of adrenal insufficiency between prednisone and dexamethasone. In one study, the children who

received prednisone recovered faster than the children receiving dexamethasone. A different study showed that treatment with fluconazole lengthens the duration of adrenal insufficiency (Table 2) [22,23].

Table 2. Glucocorticoid's anti-inflammatory activity and potential of HPA Axis suppression [18]

Glucocorticoid	Equivalent dose (mg	Glucocorticoid potency	HPA Suppression	Plasma half life (min)
Short acting				
Cortisol	20	1,0	1,0	90
Cortisone	25	0,8	No data	80-118
Intermediate acting				
Prednisone	5	4,0	4,0	60
Prednisolone	5	5,0	No data	115-200
Triamcinolone	4	5,0	4,0	30
Methylprednisolone	4	5,0	4,0	180
Long acting				
Dexamethasone	0,75	30	17	200
Betamethasone	0,6	25-40	No data	300

Simbolon et al. [24] performed a study regarding adrenal suppression in 24 children with ALL in Indonesia. For 7 weeks, the patients were given dexamethasone or prednisone therapy according to 2013 Indonesian ALL chemotherapy protocol. In standard risk group (prednisone), adrenal suppression occurred in day-56 while in high risk group (dexamethasone), significant decrease in cortisol level occurred on day-14, day-28, and day-42 from the day-0 of induction phase (p=0.001). Dexamethasone caused lower cortisol level than prednisone during chemotherapy induction phase as can be seen in previous study [24]. Another study with the same population also showed the decrease of cortisol level after prednisone therapy on the week-10 with a reduction percentage of 53% compared with cortisol level in the week-0 (p=0.027). A 64% increase occurred on week-12 in comparison to week-10 (p=0.003). Prednisone did not cause adrenal suppression during the induction phase, while cortisol decrease in consolidation phase is only temporary [25].

Other study showed that around 50% of the children experienced adrenal suppression 2 weeks after induction therapy for 4 weeks using prednisolone and the suppression effect will last for 20 weeks [26]. Similar result was also reported regarding the existence of adrenal suppression in 7 weeks after the administration of dexamethasone and prednisolone. On 4 patients treated with prednisolone, adrenal insufficiency lasted up to 2,5-4 months, while on 3 patients treated with dexamethasone, the insufficiency lasted up to 4-8 months [27]. Meanwhile, another study showed that adrenal function completely recovered in all patients in 10 weeks, and there was no difference between patients treated with prednisone and those treated with dexamethasone. Nearly 35% of children with impaired cortisol level showed signs or symptoms of adrenal insufficiency, and one children experienced adrenal crisis (table 3) [28].

Table 3. Duration of HPA Axis suppressionon the use of single dose glucocorticoids [29]

Glucocorticoids	Duration of HPA Axis suppression (day)
Short acting	
Hidrocortisone (cortisol) 250 mg Cortison 250 mg	1,25-1,5 1,25-1,5
Intermediate acting	

Prednisone 50 mg Prednisolone 50 mg Methylprednisolone 40 mg Triamcinolone 40 mg	1,25-1,5 1,25-1,5 1,25-1,5 2,25
Long-acting	
Dexamethasone 5 mg Betamethasone 6 mg	2,75 3,25

Prednisone use in nephrotic syndrome is very effective and has been used by many since 1950 to induce diuresis in order to reduce edema and proteinuria [30]. A study which analyzed HPA axis suppression of patients with nephrotic syndrome after long-term low dose alternate day prednisolone resulted in 62.5% of the patients having a peak serum cortisol concentration of <500 nmol/l, which suggested suboptimal cortisol secretion and possible HPA suppression [31]. However, another study in which the patients received long-term high dose prednisone showed that HPA axis suppression did not occur in induction and alternating phase, which were shown by the normal mean of ACTH level in both phases. It was also supportedby the absence of clinical or laboratory data which showed signs of HPA axis suppression [32].

In regards of autoimmune diseases like SLE and rheumatoid arthritis, glucocortioid has the possibility of influencing immune response and inflammation on various stages of RA [19,33]. On a study in pediatric patients with rheumatic disorder, there was more than 50% patients which experienced adrenal suppression (AS) after GC discontinuation eventhough it had been done in a gradual tappering. AS lasted more than 7 months on fifity percents of children with rheumatic disorder and more than a year in a few cases [21]. Children with severe Kawasaki's disease which received intravenous immunoglobulin (IVIG) therapy in addition to prednisolone in which the prednisolone was given for 20 days showed adrenal suppression. Morning cortisol and ACTH values after the discontinuation of prednisolone treatment were suppressed. Peak cortisol values at the first CRH stimulation test ranged from 5.1 to 25.4 µg/dL and were less than 20 µg/dL in 17 of 21 patients($r=0.727$, $p<0.001$), but were restored to more than 14.6 µg/dL in all patients by 6 months after the prednisolone treatment[34].

In pediatric patients with inflammatory bowel disease (IBD), adrenal suppression can occur in at least one fifth of the patients, even with prior tapering of glucocorticoid, based on cortisol serum measurement [35]. A study of infants with hemangioma who received prednisolone with the initial dose of 2- 3 mg/kg/day for 4 weeks, followed by tapering with the duration of GC treatment of 7,2 months showed that upon corticotropin examination, adrenal function of all control subjects were within normal limits. Hereby the conclusion that infants with hemangioma has low risk of developing adrenal insufficiency after GC therapy completion (Table 4) [36].

Table 4. Adrenal suppression events after glucocorticoids administration from various studies

Disease	**Drugs**	**Patients**	**Dose**	**Duration**	**Number of Adrenal Insuficiency**
ALL [24]	Prednisone	9	60 mg/m^2 (day 0-7) Followed by 40 mg/m^2 (day8-49)		Cortisol level Day 0: 0/9; Day 14: 1/9; Day 28 : 1/7; Day 42: 0/7; Day 56: 1/6
	Dexamethasone	15	6 mg/m^2	49 days	Cortisol level Day 0: 0/15; Day 14: 8/15; Day 28 : 9/12; Day 42: 7/11; Day 56: 0/7

ALL[25]	Prednisone	13	40 mg/m^2/day	49 days	Week 4: 0/13; Week 5:0/13; Week 6 : 0/13; Week 7: 0/13; Week 8 : 1/12; Week 10 : 1/11; Week 12: 0/10
ALL[26]	Prednisolone and dexamethasone	24	40 mg/m^2 per day)	28 days	LD-ACTH test Week 2 : 11/24 (46%) ; Week 4: 9/24 (38%); Week 8: 7/24 (29%); Week 20: 3/24 (13%)
ALL [27]	Prednisolone	10	60 mg/m^2/day	5 weeks	ACTH level 1 week: 7/10; 3 weeks: 6/10; 7 weeks: 4/10; End of follow up: 4/10
	Dexamethasone	7	10 mg/m^2/day	3 weeks	1 week: 5/7; 3 weeks: 4/7; 7 weeks: 3/7; End of follow up: 3/7
ALL[28]	Prednisone (d1-7) followed by dexamethasone	40	60 mg/m^2 10 mg/m^2/day	days 1-7 day 8-29	LD-ACTH test 1 day : 32/40 7-14 day: 8/32 28 day: 5/8 42 day : 5/5 10 weeks: 0/5
	Prednisone	24	60 mg/m^2/day	day 8-29	LD-ACTH test 1 day : 20/24 7-14 day: 4/20 28 day: 3/4 42 day : 3/3 10 weeks: 0/3
Nephrotic Syndrome[32]	Predisone	15	2 mg/kg/d or 60 mg/m^2/d followed by alternating dose 1.5 mg/kg/d or 40 mg/m^2/d	4 weeks	ACTH level Day 21: 0/15 Day 47: 0/15
Hemangioma [36]	Prednisolone	16	2 to 3 mg/kg/d then tapering	4 weeks Duration 7, 2 month	Day 13: 1/16 (6%)
Rheumatic Diseases [21]	Prednisone (30) prednisolone (1)	31	4 weeks of GC treatment		Weeks 4: 17/31 (54,8%)
Inflammatory bowel disease (IBD) [35]	Prednisolone	59	(10 mg, 5 mg) 5 mg on alternate days	5 weeks	End of follow up: 12/59 (20%)

Inhaled Glucocorticoid

Inhaled corticosteroid (ICS) is widely used as the first line treatment for respiratory diseases in children such as asthma, cystic fibrosis, and allergic rhinitis [37,38]. Ideal corticosteroid should exhibit high pulmonary deposition and residency time, low systemic bioavailability and rapid systemic clearance. Pulmonary deposition is influenced not only by inhalation devices and type of propellant (HFA atau chlorofluorocarbon), but also by aerosol preparation in the form of solution or suspension, and the particle size of inhaled fraction. Drug bioavailability depends on oral bioavailable fraction and the amounts of drug directly absorbed from pulmonary blood vessels [39]. Around 10-60% of ICS are administered through metered dose inhaler to the lungs, and some were left in the oropharynx and were

swallowed [40]. The residue from inhalation are usually swallowed and absorbed in the gastrointestinal tract. At low dose, this compound is generally considered safe; however, high dose consumption for a long period of time is associated with risks of systemic effects (Table 5) [5].

Table 5. Pharmacologic properties of inhaled Glucocorticoid [18,44]

Drug	Receptor Binding Affinity	Lung Delivery	Oral Bioavailability (%)	Protein Binding (%)	Systemic Clearance (L/h)	Distribution volume (L)	Half life inhaled (h)
Budesonide	9,4	15-30	11	88	84	280	2
Fluticasone propionate	18	20	≤1	90	66	318-859	14,4
Flunisonide	1,8	68	20	80	58	96	1,6
Beclomethasone dipropionate/17-monopropionate	0,4/13,5	50-60	20/40	87	150/120	20/424	Unknown/2,7
Ciclesonide/ desciclesonide	0.12/12	50	<1/<1	99/99	152/228	207/897	0,5/4,8
Mometasone furoate	23	11	<1	99	53	152	Unknown
Triamcinolone acetonide	3,6	22	23	71	45-69	103	3,6

Prevalence of adrenal suppression in ICS use is also influenced by the ICS's potency, dose, treatment duration, delivery method, drug interactioin and site of drug activation [40,41]. The likelihood of HPA axis suppression increased in accordance with ICS dosage (OR 1.005, 95% CI 1.003-1,.009, P<0.001) [42]. A study identified the genetic variants which affect susceptibility towards adrenal suppression triggered by corticosteroid. Adrenal suppression happens in 7% of children, and this is related with genetic variance in the PDGFD gene locus which increases the risk of adrenal suppression due to corticosteroid use [43].

A Canadian study involved >2500 pediatrician to report new cases with the symptoms of adrenal suppression (AS). In a matter of 2 years, there were forty six identified cases of AS with the estimated annual incidence 0.35 /100.000 children aged 0-18 years (95% CI 0.26-0.47). The most common symptom is growth failure (35%), non-specific symptoms (28%) or both (13%). 80% (thirty seven children) with symptoms of adrenal insufficiency received GC through inhalation route only or combined with other route, and adrenal crisis was reported to happen on six cases (13%) [45]. A study from South Africa reported the prevalence of HPA suppression of 35 (CI=17-56%) out of 26 children with asthma [46].

A study in England that spread 2912 questionnaires to endocrinologists for adult and pediatrician, reported 33 cases which fulfil the diagnosis of abnormal HPA axis functioning. Out of the 33 cases, 91% received fluticasone, 3% received fluticasone and budesonide, and 6% received beclomethasone [47]. On meta-analytical study it was found that fluticasone is the most common ICS associated with HPA axis suppression in children and adults. HPA axis suppression was found in 6, 7, 10 and 13 percents of the patients, which received 500, 1000, 1500 and 2000 lg /day of fluticasone, respectively [40].

A systematic review and meta-analysis evaluated the effect of inhaled GC towards the suppression of endogenous cortisol in terms of suppression of urinary cortisol. From the analysis of the 64 identified studies, the strongest

dosage response observed for the suppression of urinary cortisol was found in patients treated with beclomethasone, followed by those treated with fluticasone and budesonide, while there was no significant cortisol suppression associated with the treatment using ciclesonide [48].

CONCLUSION

Glucocorticoids are produced by the adrenal gland cortex and are secreted into systemic circulation in a circadian rhythm. These steroid hormones play many roles in physiological systems in the body, for example in response to stress, immune system, inflammatory regulation, carbohydrate metabolism, protein breakdown, blood electrolyte levels, and behavior. Glucocorticoids may be given systemically or by other routes such as topical, ophthalmic, inhalation, nasal, and intra-articular administration. Exogenous glucocorticoid administration may suppress the hypothalamic-pituitary-adrenal (HPA) axis either through oral or inhaled routes. Complications of systemic glucocorticoid therapy increase, in proportion to the increase in dose, duration of therapy and frequency of administration

The onset and duration of adrenal insufficiency vary between previous studies but the frequency is fairly high in both systemic and inhaled glucocorticoids usage during therapy and after its discontinuation. Generally, suppression of HPA axis will revert if glucocorticoids are used less than 10-14 days. However, if glucocorticoids are used for 2 weeks or more, laboratory testing of potential HPA axis suppression is required. To avoid complications, careful monitoring of patients and gradual glucocorticoid tapering is necessary in order to minimize adrenal crisis occurrence.

AUTHORS' CONTRIBUTION

Both the authors have contributed equally for bringing this review article effectively.

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest.

REFERENCES

[1] E Bayman; AJ Drake. *Arch Dis Child Month*. **2016.**

[2] BG Katzung; AJ Trevor. Basic & Clinical Pharmacology 13th edition. New York: McGraw-Hill Education. **2015.**

[3] AK Younes; NK Younes. *Translational Pediatrics*. **2017,** 17, 6(4), 269-273.

[4] W Ericson-Neilsen; AD Kaye. *Steroids* . **2014,** 14, 2.

[5] RM Paragliola; G Papi; A Pontecorvi; SM Corsello. *Int J Mol Sci*. **2017,** 18, 2201.

[6] M Oray; K Abusamra; N Ebrahimiadib; H Meese; S Foster. *Expert Opinion on Drug Safety*. **2016.**

[7] LP Seguro; C Rosario; Y Shoenfeld. *Autoimmunity Reviews*. **2012.**

[8] F Aljebab; I Choonara; S Conroy. *Arch Dis Child Y***. 2016,** 101, 365-370.

[9] A Ahmet; H Kim; S Spier. *Allergy, Asthma Clin Immunol*. **2011,** 7, 13.

[10] D Liu; A Ahmet; L Ward; P Krishnamoorthy; ED Mandelcorn; R Leigh. *Allergy, Asthma Clin Immunol.* **2013,** 9, 30.

[11] A Caplan; N Fett; M Rosenbach; V Werth; RG Micheletti. *J Am Acad Dermatol*. **2017,** 76, 11-16.

[12] AC Mendoza-Cruz; O Wargon; S Adams; H Tran; CF Verge. **2013,** 98(12), E1936-E1940.

[13] MJ Garabedian; CA Harris; F Jeanneteau. *F1000 Research*. **2017,** 6, 1208.

[14] BP Schimmer; JW Funder. Adrenocorticotropic Hormone, Adrenal Steroids, and the Adrenal Cortex. Dalam L. L. Brunton (Penyunt.), Goodman & Gilman's The Pharmacological Basis of Theurapeutics (13 th edition ed., hal. 845-863). New York: by McGraw-Hill Education. **2018.**

[15] EJ Barrett. Medical Physiology. *A Cell Mol App. Philadelphia: Elsevier Saunders.* **2012,** 1057-1073.

[16] S Chung; GH Son; K Kim. *Biochimica et Biophysica Acta*. **2011,** 1812, 581-591.

[17] DG Gardner ; D Shoback. Greenspan's Basic & Clinical Endocrinology Tenth Edition. New York, United States: McGraw-Hill Education. **2018.**

[18] G Chrousos; A Pavlaki; M Magiakou. Glucocorticoid Therapy and Adrenal Suppression. Endotext. **2011.**

[19] N Goulding; R Flower. *Glucocorticoids*. Basel: Birkhăuser Verlag.

[20] A Seth; A Aggarwal. Monitoring Adverse Reactions to Steroid Therapy in Children. *Ind Pediatrics*. **2004,** 41.

[21] A Ahmet; V Brienza; A Tran; J Lemieux; M Aglipay; N Barrowman. *Arthritis Care Res*. **2016.**

[22] M Gordijn; N Rensen; R Gemke; V Dalen; E Rotteveel J; G Kaspers. *Cochrane Database of Syst Rev*. **2015,** 8, CD008727.

[23] N Rensen ; RJ Gemke; EC Van Dalen; J Rottevee; GJ Kaspers. *Cochrane Database of Syst Rev*. **2017,** 11, CD008727.

[24] O Simbolon; I Yulistiani Ugrasena; M Qibtiyah. *Folia Medica Indones*. **2016,** 52, 7-13.

[25] A Amarullah; D Hasmono; I Ugrasena; Yulistiani. *Folia Medica Indones*. **2018,** 54, 59-63.

[26] P Mahachoklertwattana; S Vilaiyuk; S Hongeng; C Okascharoen. *J Pediatr*. **2004,** 144, 736-40.

[27] KB Petersen; J Muller; M Rasmussen; K Schmiegelow. *Med Pediatric Oncol*. **2003,** 41, 110-114.

[28] S Einaudi; N Bertorello; N Masera; L Farinasso; E Barisone; C Rizzari. *Pediatric Blood Cancer*. **2008,** 50, 537-541.

[29] GK McEvoy. AHFS drug information, New & Revised Drug Monograph . United States of America: American Society of Health-System Pharmacists. **2013.**

[30] E Hodson; J Knight; N Willis; J Craig. *The Cochrane Collaboration*. **2004.**

[31] AS Abeyagunawardena; P Hindmarsh; RS Trompeter. *Arch Dis Child*. **2007,** 92, 585-588.

[32] RN Hapsari; N Asmaningsih; E Padolo; Yulistiani. *Int J Pharma Clin Res*. **2017,** 9(4), 317-323.

[33] G Saggese; F Vierucci. Systemic Corticosteroids for Inflammatory Disorders in Pediatrics (hal. 3-9). London: Springer International Publishing. **2015.**

[34] M Goto; N Miyagawa; K Kikunaga; M Miura; Y Hasegawa. *Endocrine J*. **2015,** 62 (2), 145-151.

[35] M Sidoroff; KL Kolho. *BMC Gastroenterol*. **2014.**

[36] JP Lomenick; KL Reifschneider; AW Lucky; D Adams; G Richard; M Azizkhan; JG Woo. *Arch dermatol.* **2009,** 145.

[37] JH Toogood. Glucocorticoids. **2001,** 162-168.

[38] CR Kapadia; TD Nebesio; SE Myers; S Willi; BS Miller; DB Allen. *JAMA Pediatrics*. **2015.**

[39] T Gulliver; R Morton; N Eid. *Pediatr Drugs*. **2007,** 9 (3), 185-194.

[40] LN Bondugulapati; DA Rees. *Clinical Endocrinol*. **2016,** 0, 1-5.

[41] HW Kelly. *Annals of Pharmacother*. **2009.**

[42] Leung JS; Johnson DW; Sperou AJ; Crotts J; Saude E; Hartling L. *PLoS ONE***. 2017,** 12(8), e0182738.

[43] RW Smith; K Downey; M Gordon; A Hudak; R Meeder; S Barker. *Paediatr Child Health*. **2012,** 17(5), e34-e39.

[44] DB Hawcutt ; B Francis; DF Carr; AL Jorgensen; P Yin; N Wallin. *Lancet Respir Med*. **2018,**

[45] EB Goldbloom; A Mokashi; EA Cummings ; S Abish; SM Benseler; HQ Huynh. *Arch Dis Child.* **2016,** 0, 1-6.

[46] EW Zöllner; C Lombard; U Galal; S Hough; E Irusen; E Weinberg. *J Pediatr Endocr Met.* **2011,** 24(7-8), 529-534.

[47] GR Todd; CL Acerini; R Ross-Russell; S Zahra; JT Warner; D McCance. *Arch Dis Child*. **2002,** 87, 457-461.

[48] ML Kowalski ; P Wojciechowski; M Dziewonska; P Rys. *Allergy Asthma Proceed.* **2016.**