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Communication

Exploring Glucocorticoid Safety: Insights from pKCSM Predictions on Tolerability and Toxicity Profiles

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Abstract: This comprehensive analysis aims to offer valuable insights into the safety profiles of these glucocorticoids, facilitating the identification of compounds with potentially reduced adverse effects. This study investigates the toxicity profiles of various glucocorticoids, utilizing predictions from the pKCSM Server. Among the glucocorticoids examined, Dexamethasone, Triamcinolone, Hydrocortisone hemisuccinate, Paramethasone, Fluprednisolone, and Flumethasone emerge as potentially less toxic, displaying favorable scores across diverse parameters such as Max. Tolerated Dose (human, MRT), Oral Rat Acute Toxicity (LD50), and Oral Rat Chronic Toxicity (LOAEL). Notably, Hydrocortisone hemisuccinate and Triamcinolone stand out for their high tolerability capacity based on the Max. Tolerated Dose (human, MRT), suggesting enhanced safety profiles. These findings contribute insights into selecting glucocorticoids with optimal safety and tolerability for potential therapeutic applications.Further research and clinical investigations are warranted to validate and refine these findings, ensuring the responsible and effective use of glucocorticoids in medical practice.

Keywords: Max. tolerated dose; triamcinolone; oral rat acute toxicity (LD50); pKCSM server

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1. Introduction

Glucocorticoids represent a category of steroid hormones which in the human body are mainly produced in the fascicular area of the adrenal cortex. Their secretion is activated by adrenocorticotropic hormone (ACTH), produced by the adenohypophysis, which in turn is stimulated by corticotropin-releasing hormone (CRH) produced by the hypothalamus. The main glucocorticoid is cortisol, the secretion of which increases in response to stress, both physical and emotional [1,2].

This makes glucocorticoids crucial in the body's adaptation to stressful situations. In modern pharmacology, there are numerous synthetic glucocorticoids, including prednisone.The action of glucocorticoids extends to the metabolism of carbohydrates, lipids and proteins, simultaneously reducing inflammatory and immune responses [3,4]. Synthetic glucocorticoids exhibit diverse affinities for glucocorticoid and mineralocorticoid receptors, distinct from cortisol.

Specific structural modifications are employed to extend the half-life of these synthetic compounds. These structural adjustments aim to enhance glucocorticoid receptor binding selectivity while diminishing affinity for mineralocorticoid receptors. Such selectivity is crucial to mitigate undesired effects associated with mineralocorticoid receptor activation, which plays a role in electrolyte and water balance regulation [5-7].

Glucocorticoids, due to their steroid nature, are readily absorbed following oral administration. Topical use (cutaneous, ocular, or via inhalation) presents variable and challenging-to-assess absorption kinetics.

Glucocorticoids are categorized based on their duration of action, distinguishing between short-acting, intermediate-acting, and long-acting synthetic glucocorticoids [8-14].

- *Short-acting synthetic glucocorticoids* include:

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Prednisone
Prednisolone
Methylprednisolone
Meprednisone

- *Intermediate-acting synthetic glucocorticoids* include:
Triamcinolone
Paramethasone
Fluprednisolone
- *Long-acting synthetic glucocorticoid*s include:
Betamethasone
Desametasone

The objective of this theoretical study is to assess the toxicity of approximately 30 glucocorticoids by employing various prediction parameters through the pkCSM Server [15]. The evaluation will focus on identifying the glucocorticoid with the least toxicity, considering key parameters such as AMES toxicity, Max. tolerated dose in humans (log mg/kg/day), Oral Rat Acute Toxicity (LD50 in mol/kg), Oral Rat Chronic Toxicity (LOAEL in log mg/kg_bw/day), Hepatotoxicity, and Skin Sensitisation.

2. Material and Methods

18-Hydroxycorticosterone, Corticosterone, Desoxycortone, Fluocortolone, HydrocortisoneAcetate, Medrysone, Prednisolone, Cortisol, Dexamethasone, Fluorometholone, Methylprednisolone, Triamcinolone, Fluoxymesterone, Cortisone, Paramethasone, Betamethasone, Cortodoxone, Fluprednisolone, Budesonide, Flumethasone are evaluated by pkCSM Server[15].

3. Results and Discussion

The primary focus of this evaluation is to pinpoint the glucocorticoid demonstrating the least toxicity, taking into account critical parameters such as AMES toxicity, Max. tolerated dose in humans (log mg/kg/day), Oral Rat Acute Toxicity (LD50 in mol/kg), Oral Rat Chronic Toxicity (LOAEL in log mg/kg_bw/day), Hepatotoxicity, and Skin Sensitisation. This comprehensive analysis aims to provide insights into the safety profile of these glucocorticoids, aiding in the identification of compounds with potentially lower adverse effects.

Based on the prediction results of the main toxicity parameters of glucocorticoids using pKCSM, a notable observation is that a significant portion of them exhibits a very low tolerability capacity, as indicated by the Max. Tolerated Dose (human) (log mg/kg/day), often yielding negative scores. According to pKCSM, a lower Max. Tolerated Dose (MRTD) score, particularly minor around -0.477 (log mg/kg/day), is considered indicative of low tolerability capacity.

Another shared characteristic among these glucocorticoids, highlighted by pKCSM predictions, is their potential excellence in terms of AMES toxicity, Hepatotoxicity, and Skin Sensitization. The results of these tests suggest a favorable safety profile for the glucocorticoids under consideration, indicating a lower likelihood of causing mutagenic effects (AMES toxicity), liver toxicity (Hepatotoxicity), and skin sensitization. This shared positive outlook across multiple toxicity parameters further supports the potential suitability of these glucocorticoids, underscoring their safety attributes in crucial aspects of toxicological evaluation.

Based on the comprehensive evaluation of various toxicity parameters using the pKCSM Server, seven glucocorticoids emerge as relatively less toxic. These include Dexamethasone, Triamcinolone, Hydrocortisone hemisuccinate, Fluprednisolone, and Paramethasone. The consistent favorable outcomes across multiple toxicity parameters suggest that these glucocorticoids may possess a more favorable safety profile compared to others in the investigation.

The main results of each of them are reported below:

Dexamethasone:

Max. Tolerated Dose (human, MRT): 0.097 log mg/kg/day

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Oral Rat Acute Toxicity (LD50): 2.504 mol/kg
Oral Rat Chronic Toxicity (LOAEL): 2.541 log mg/kg_bw/day
Triamcinolone:
Max. Tolerated Dose (human, MRT): 0.347 log mg/kg/day
Oral Rat Acute Toxicity (LD50): 2.612 mol/kg
Oral Rat Chronic Toxicity (LOAEL): [Inserire il valore mancante]
Hydrocortisone hemisuccinate:
Max. Tolerated Dose (human, MRT): 0.398 log mg/kg/day
Oral Rat Acute Toxicity (LD50): 2.516 mol/kg
Oral Rat Chronic Toxicity (LOAEL): 2.475 log mg/kg_bw/day
Paramethasone:
Max. Tolerated Dose (human, MRT): 0.022 log mg/kg/day
Oral Rat Acute Toxicity (LD50): 2.367 mol/kg
Oral Rat Chronic Toxicity (LOAEL): 2.504 log mg/kg_bw/day
Fluprednisolone:
Max. Tolerated Dose (human, MRT): 0.024 log mg/kg/day
Oral Rat Acute Toxicity (LD50): 2.603 mol/kg
Oral Rat Chronic Toxicity (LOAEL): 1.98 log mg/kg_bw/day
Flumethasone:
Max. Tolerated Dose (human, MRT): 0.07 log mg/kg/day
Oral Rat Acute Toxicity (LD50): 2.684 mol/kg
Oral Rat Chronic Toxicity (LOAEL): 2.596 log mg/kg_bw/day
Fluprednisolone:
Max. Tolerated Dose (human, MRT): 0.024 log mg/kg/day
Oral Rat Acute Toxicity (LD50): 2.603 mol/kg
Oral Rat Chronic Toxicity (LOAEL): 1.98 log mg/kg_bw/day

Tolerated Dose (human, MRT) is a critical parameter, and the results indicate that Hydrocortisone hemisuccinate and Triamcinolone exhibit a notable high tolerability capacity. This suggests that these two glucocorticoids may be considered favorable in terms of human tolerability, as reflected in their ability to be administered at higher doses with reduced risk of adverse effects.

This distinguishing feature underscores the importance of considering not only the therapeutic efficacy but also the safety and tolerability profiles when evaluating glucocorticoids for medical applications.

Table 1. shows of investigation of the toxicity profiles of various glucocorticoids, utilizing predictions from the pKCSM Server.

Compounds	AMES toxicity	Max. tolerated dose (human) (log mg/kg/day)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity	Skin Sensitisation	T. Pyriformis toxicity (log ug/L)	Minnow toxicity (log mM)
18-Hydroxycorticosterone	No	-0.427	1.975	2.592	no	no	0.338	1.827
Corticosterone	No	-0.694	1.937	1.545	no	no	0.624	1.237
Desoxycortone	No	-1.105	2.439	1.78	no	no	0.83	0.412
Fluocortolone	No	-0.576	2.073	1.95	no	no	0.515	1.851
Hydrocortisone Acetate	No	-0.6	2.218	1.757	no	no	0.382	1.385
Medrysone	No	-0.996	1.889	1.724	no	no	0.978	0.695
Prednisolone	No	-0.076	2.538	0.747	no	no	0.338	2.439
18-Oxocortisol	No	-0.265	2.119	2.626	no	no	0.292	2.364
Cortisol	No	-0.183	2.088	2.504	no	no	0.312	1.944
Dexamethasone	**No**	**0.097**	**2.504**	**2.541**	**No**	**No**	**0.299**	**2.535**
Fluorometholone	No	-0.413	2.329	1.698	No	No	0.473	2.179
Hydrocortisone Butyrate	No	-0.748	2.197	1.964	No	No	0.376	1.513

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Methylprednisolone	No	-0.183	2.143	0.654	No	No	0.345	1.934
Triamcinolone	**No**	**0.347**	**2.612**	**2.475**	**No**	**No**	**0.286**	**4.181**
Aldosterone	No	-0.616	1.928	2.263	No	No	0.433	1.558
Cortisone	No	-0.35	2.146	2.197	No	No	0.337	1.759
Fludrocortisone Acetate	yes	-0.32	2.588	1.836	No	No	0.305	2.726
Fluoxymesterone	No	-0.073	2.005	1.427	No	No	0.537	2.012
Hydrocortisone hemisuccinate	**No**	**0.398**	**2.516**	**2.425**	**No**	**No**	**0.285**	**2.681**
Paramethasone	**No**	**0.022**	**2.367**	**2.504**	**No**	**No**	**0.302**	**2.471**
Betamethasone	No	-0.632	2.732	2.742	No	No	0.29	2.675
Cortodoxone	No	-0.212	1.938	1.457	No	No	0.417	0.951
Fludrocortisone	No	-0.059	2.544	2.519	No	No	0.296	2.621
Fluprednisolone	**No**	0.024	2.603	1.98	**No**	**No**	0.313	3.111
Hydrocortisone phosphate	yes	-0.687	2.559	2.871	No	No	0.285	2.169
Budesonide	No	-0.589	1.922	2.131	No	No	0.29	0.956
Desoximetasone	No	-0.504	2.172	1.937	No	No	0.479	1.927
Flumethasone	**No**	0.07	2.684	2.596	**No**	**No**	0.294	3.192
Halometasone	No	-0.199	2.309	2.503	No	No	0.289	2.446
Hydrocortisone Valerate	No	-0.794	2.133	1.971	No	No	0.374	1.319
Prednisolone Acetate	yes	-0.591	2.18	1.772	No	No	0.381	1.464

4. Conclusion

In conclusion, the evaluation of various glucocorticoids using predictions from the pKCSM Server has provided valuable insights into their toxicity profiles. Among the glucocorticoids studied, Dexamethasone, Triamcinolone, Hydrocortisone hemisuccinate, Paramethasone, Fluprednisolone, and Flumethasone exhibit promising characteristics, suggesting potential lower toxicity compared to others.

A noteworthy feature is the high tolerability capacity observed in Hydrocortisone hemisuccinate and Triamcinolone, particularly evident in their Max. Tolerated Dose (human, MRT). This emphasizes their favorable safety profiles, indicating the ability to be administered at higher doses with reduced risk of adverse effects.

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