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Chronopharmacology of Glucocorticoids

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Abstract

Glucocorticoids influence a wide array of metabolic, anti-inflammatory, immunosuppressive, and cognitive signaling processes, playing an important role in homeostasis and preservation of normal organ function. Synthesis is regulated by the hypothalamic-pituitary-adrenal (HPA) axis of which cortisol is the primary glucocorticoid in humans. Synthetic glucocorticoids are important pharmacological agents that augment the anti-inflammatory and immunosuppressive properties of endogenous cortisol and are widely used for the treatment of asthma, Crohn's disease, and rheumatoid arthritis, amongst other chronic conditions. The homeostatic activity of cortisol is disrupted by the administration of synthetic glucocorticoids and so there is interest in developing treatment options that minimize HPA axis disturbance while maintaining the pharmacological effects. Studies suggest that optimizing drug administration time can achieve this goal. The present review provides an overview of endogenous glucocorticoid activity and recent advances in treatment options that have further improved patient safety and efficacy with an emphasis on chronopharmacology.

Keywords

Cortisol; synthetic glucocorticoids; chronopharmacology; chronopharmacokinetics; HPA axis disruption; circadian rhythms

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Declaration of Interest Statement

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1 Introduction

Glucocorticoids are a group of cholesterol-derived hormones secreted from the adrenal glands. They are involved in a wide array of metabolic, anti-inflammatory, immunosuppressive, and cognitive signaling processes with the discovery of such properties by Hench and Kendal in 1948 [1–3]. Glucocorticoids are thought to be the most important mediators of systemic inflammation and play an essential role in restoring homeostasis [4]. Glucocorticoids help maintain the proper balance between proinflammatory and anti-inflammatory mediators, which can be upset by serious infections and diseases [5, 6]. Cortisol, the primary glucocorticoid in humans, and its precursors vary in a predictable time-dependent manner in humans with both circadian and ultraradian patterns of secretion and elimination [4, 7]. The oscillatory behavior is driven by signals received from the central pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) and external cues, such as stress [8, 9]. Cortisol is a key entraining signal for synchronization of peripheral circadian clock genes that coordinate various biological processes across their residing tissues to ensure homeostasis [10–13]. Glucocorticoids impact the rhythmic expression of circadian genes in almost all tissues [14]. The maintenance of proper circadian rhythmicity is critical in humans with peak cortisol concentrations in the early morning and nadirs at night [7, 15]. The timing of the peak concentration is highly regulated and in conjunction with other signaling hormones enables the separation of physiological processes throughout the day for optimal biological functioning and survival [11, 13, 16]. The natural rhythms of plasma cortisol are sensitive to internal physiological and external environmental cues which can lead to altered or disrupted oscillations throughout the day. Phase shifts, atypical absolute concentrations, and dampened or heightened amplitudes are all indicators of a disrupted diurnal rhythm [12]. For example, clinically significant increases in glucose and insulin occur with misalignment of the cortisol rhythm compared to normal cortisol activity [14].

Synthetic glucocorticoids are an important class of pharmacological agents to augment or substitute, in the case of adrenal insufficiency, the anti-inflammatory and immunosuppressive properties and physiological actions of endogenous glucocorticoids [17–19]. Despite the abundance of clinical benefits and years since its first clinical use in the 1950s, glucocorticoid therapies are associated with serious adverse effects, especially during high-dose administration [20–24]. Patients are at a risk of a host of clinical manifestations, including psychiatric disorders like depression, drug-induced hyperglycemia, long-term diabetes mellitus, glaucoma, osteoporosis, obesity, gastritis and cardiovascular disease [6, 14, 22, 25–31]. The systemic effects arise from the pleiotropic influence of glucocorticoids on liver, skeletal muscle, adipose tissue, and pancreatic functioning, amongst other tissues [32]. Glucocorticoids influence carbohydrate metabolism, inhibit gluconeogenesis, modulate lipid disposition and storage, inhibit processes such as proinflammatory cytokine production in response to injury and pathogens, and regulate proinflammatory mediators under normal physiological conditions [33, 34]. Furthermore, glucocorticoids regulate blood pressure, bone resorption, the cell cycle, and energy homeostasis [35]. High glucocorticoid levels during the day facilitate energy allocation to the brain, muscles, and immunosurveillance while low levels during the night facilitate activation of the immune system [16, 33].

Although widely accepted as the leading treatment option for a host of health conditions over the last century, challenges remain before glucocorticoid therapies are no longer accompanied by serious adverse effects. A major downfall of long-term term use of synthetic glucocorticoids is the modification of endogenous cortisol secretary patterns which is thought to lead to misalignment of peripheral clock genes and improper physiological functioning [10, 20, 36–38]. This unmet medical need is particularly true for patients receiving treatment for chronic conditions requiring lifetime administration, often at high doses. While significant progress has been made to understand the genomic and non-genomic actions of synthetic glucocorticoids, the mechanisms have not yet been elucidated, given that dissecting drug effect from inherent inflammatory processes is rather challenging [30, 31, 39]. Today, glucocorticoid research continues to strive for long-term treatment options that balance safety and efficacy to minimize complications as shown in Figure 1. There is interest in minimizing the disruption of the homeostatic activity of cortisol while retaining the pharmacological actions of synthetic glucocorticoids by leveraging the interplay between the HPA axis and the immune system [20, 40]. Evidence suggests that this goal can be achieved by optimizing drug administration time [41, 42]. In general, chronopharmacokinetics are most beneficial for drugs with narrow therapeutic ranges, for drugs with high variability, and to treat diseases with circadian-dependent symptomology [43]. All of which may be true for glucocorticoids, supporting the potential to improve the effectiveness and safety of treatment options through chronopharmacological intervention. This review provides an overview of the role of glucocorticoids in health and disease, as well as recent advances in pharmacology that have improved patient safety and effectiveness with an emphasis on chronopharmacokinetics and chronopharmacodynamics.

2 Overview of glucocorticoid activity: the key aspects of systemic and tissue-level regulation

2.1 Synthesis of Glucocorticoids

Glucocorticoid synthesis is regulated by the hypothalamic-pituitary-adrenal (HPA) axis in which cortisol, the final HPA axis product, is the primary glucocorticoid in humans [3, 20]. The HPA axis is the principal stress response mechanism, both physical and physiological, along with the autonomic nervous system, constituting a carefully regulated signaling network [44, 45]. The HPA axis consists of stimulatory signals and negative feedback loops which are important for maintaining both resting and stress-related homeostasis, and for preserving the normal physiology of organ systems and almost all physiologic, cellular and molecular networks [46, 47]. When an individual is exposed to stress, the HPA axis becomes activated, leading to an increase in cortisol secretion, which along with other mediators, facilitates the modification of underlying physiological properties in the body and brain for maintenance of homeostasis, a process referred to as allostasis [48, 49]. A schematic of the HPA axis is given in Figure 2. The release of corticotrophin-releasing hormone (CRH) in the hypothalamus triggers the release of adrenocorticotrophic hormone (ACTH) in the pituitary gland and finally cortisol from the adrenal glands. Cortisol, in addition to mediating downstream physiological effects, also provides negative feedback to the HPA axis by inhibiting the release of CRH and ACTH and subsequently its own secretion [50]. This negative feedback loop is important for maintaining normal physiological levels of

circulating cortisol, enabling the host to preserve homeostasis in response to stress or disease activity.

2.2 Transport of Plasma Cortisol

Once secreted from the adrenal glands, cortisol is circulated throughout the host to peripheral tissues. Endogenous cortisol is highly bound (90–95%) to plasma proteins, corticoid binding globulin (CBG or transcortin) and albumin, which influence the half-life, storage and volume of distribution of circulating cortisol [53–55]. Cortisol has a typical half-life of 70 to 120 minutes [3]. Protein-bound cortisol is circulated throughout the host to various tissues and is subsequently liberated from CBG by elastase. Upon its release, cortisol can freely cross cell membranes due to its lipophilic nature and bind to cytosolic glucocorticoid receptors [29, 56]. Only free, unbound cortisol is considered to be biologically active [45, 55]. Furthermore, CBG exhibits its own circadian rhythmicity that is in antiphase with the circadian patterns of cortisol secretion [7]. Unbound cortisol concentrations outside the physiological range may in part be due to disturbances in the time course of CBG [54, 55].

2.3 Glucocorticoid Receptors

Unbounded cortisol freely crosses the cell membranes of immune and other cell types, where many of cortisol's physiological actions are regulated by glucocorticoid receptors. Upon binding in the cytoplasm, the bound glucocorticoid-receptor complex undergoes a transformational change and translocates to the nucleus where subsequent regulation of gene transcription occurs through glucocorticoid response elements [7, 31]. The glucocorticoid receptor (Type II) primarily regulates the anti-inflammatory effects of circulating cortisol through transrepression, or inhibition, of genes involved in the production of proinflammatory cytokines and other mediators involved in immune response [20, 29, 30, 57]. A second kind of glucocorticoid receptor (Type I) has mineralocorticoid activity and is important for maintaining fluids and electrolyte homeostasis [57, 58].

While the glucocorticoid receptor is expressed in almost all tissues, mineralocorticoid receptors are localized to the kidney, colon, salivary and sweat glands, and the hippocampus [59]. Mineralocorticoid receptors have a high affinity, but low capacity for glucocorticoids, whereas glucocorticoid receptors have low affinity, but high capacity. As such, the mineralocorticoid receptors respond to low glucocorticoid concentrations and glucocorticoid receptors respond to both basal and stress concentrations [60]. The mineralocorticoid receptor is almost always in an activated state in the nucleus and the glucocorticoid receptors remains latent in the cytoplasm until activation [7]. The balance between these receptors is believed to have important behavioral and cognitive influence in response to stress [57, 58]. Additionally, rapid non-genomic effects of glucocorticoids are explained by the activity of membrane-associated receptors [3, 7, 34]. Together, the various receptor types are responsible for maintaining the fast and slow signaling cascades controlled by glucocorticoids corresponding with the non-genomic and genomic mechanisms of action, respectively [57]. While non-genomic influences of glucocorticoids occur within minutes to hours, genomic actions mediated by glucocorticoid receptors, such as altered transcription of genes, have much longer time scales.

2.4 Enzymatic Regulation of Cortisol

Cortisol undergoes interconversion between its active and inactive forms by 11β-hydroxysteroid dehydrogenase (11β-HSD) types 1 and 2, respectively, for regulation of cortisol concentrations in peripheral tissues [45, 55]. This interconversion protects the mineralocorticoid receptor from excess cortisol-induced activity and plays an important role in modulating systemic inflammatory response [61]. Cortisol is inactivated to cortisone by 11β-HSD2 in the kidneys while 11β-HSD1 activates cortisol from cortisone in the liver, adipose and other bodily tissues [62]. Readers are directed to the review by Chapman et al. for a detailed description of the influences of 11β-HSD enzymes on glucocorticoid actions [56]. Cortisol is also metabolized by CYP3A4, an important cytochrome p450 enzyme in the liver [62]. Both cortisol and cortisone derivatives are further metabolized by reductase enzymes or conjugated to glucuronic acid, and rapidly excreted in urine [3].

3 Glucocorticoids in disease

Clinical manifestations associated with cortisol outside the normal physiological range arise from disruption of the HPA axis, which affects adrenal secretion and circulating glucocorticoids, as well as from modifications in local glucocorticoid activity that upsets normal functioning of peripheral tissues. Irregular HPA axis activity is associated with changes in the rest-activity cycle as a result of shift work or jet lag, hypersecretion due to various physiological factors (aging, sleep disorders, depression, and adrenal morbidities, etc.), the onset and pathogenesis of several inflammatory or immune conditions, and pharmacological intervention [14, 63, 64]. Adrenal insufficiency is associated with many immune and inflammatory conditions such as sepsis, severe pneumonia, adult respiratory stress syndrome, and HIV infection, as a result of both decreased cortisol secretion and impaired signal transduction, although these mechanisms are not fully understood [65]. The extent of HPA axis disruption varies from normal to complete adrenal insufficiency depending on the severity of HIV infection [66]. Similarly, chronic allergic inflammatory disorders are accompanied by reduced HPA axis activity leading to flattened diurnal rhythms and low peak concentrations of cortisol due to interactions between the stress and immune systems involved in allergic conditions [67]. Conversely, surgery and fevers due to infection are strong activators of the HPA axis, which lead to the stimulation of ACTH and cortisol secretion [64]. Several other conditions associated with prolonged disruption of the HPA axis are shown in Table 1 (adapted from [47]).

Abnormal glucocorticoid activity in peripheral tissues can arise due to local dysregulation of glucocorticoids. This dysregulation interrupts the normal signaling cascades of cortisol necessary for homeostasis. Glucocorticoid activity in peripheral tissues influences the strength of negative feedback to the HPA axis, which then induces a compensatory increase or decrease in cortisol secretion to account for differences at the tissue-level [47]. Primary generalized glucocorticoid resistance (PGGR) or Chrousos syndrome is a rare condition in which all tissues have decreased sensitivity or resistance to glucocorticoids [68]. PGGR is accompanied by hypersecretion of cortisol and its precursors due to impaired feedback to the HPA axis [69]. Conversely, primary generalized glucocorticoid hypersensitivity (PGGH) leads to increased sensitivity to glucocorticoids in all peripheral tissues and compensatory

suppression of the HPA axis [70]. While PGGR and PGGH are rare, various levels of resistance and hypersensitivities are observed in chronic inflammatory conditions [71]. Rheumatoid arthritis, lupus, asthma and AIDS have shown regular activity of the HPA axis but altered glucocorticoid activity in various tissues [72]. These irregularities are attributed to hypersensitivity or resistance to glucocorticoids in peripheral tissues due to interference by disease on glucocorticoid receptors and signal transduction [73–75]. Changes in receptor-mediated activity are a result of modified affinity, nuclear translocation, glucocorticoid response element binding and communication with transcription factors or cofactors [76]. Furthermore, patients suffering from rheumatoid arthritis or inflammatory bowel disease (IBD) have also shown increased levels of 11β-HSD1 and decreased levels of 11β-HSD2 which would lead to locally high cortisol concentrations [77]. Readers are directed to the review by Quax for further discussion of glucocorticoid sensitivity in health and disease [77] and to the reviews by Charmandari and Chrousos [47, 78] for a deeper look at the role that glucocorticoids play in maintaining homeostasis and stress management.

4 Pharmacological intervention with synthetic glucocorticoids

Synthetic glucocorticoids are widely used for the treatment of a variety of chronic conditions such as asthma, skin infections, Crohn's disease, and rheumatoid arthritis, as well as the management of immune response following organ transplantation [6, 30]. Acute exposure is associated with reduced inflammation, whereas chronic exposure has immunosuppressive action [34]. An almost immediate decline in blood lymphocytes and basophils, and an increase in neutrophils are observed after administration, while the induction of interleukins and other immunosuppression mediators, such as IκBα (inhibitor of transcription factor NFκB), are observed after several hours [79]. Importantly, the adverse phenotypes that appear following synthetic glucocorticoid administration are fundamentally the same as those associated with atypical endogenous cortisol levels [80]. Many of the adverse effects of glucocorticoid treatment are due to local excesses or deficiencies in peripheral tissues, as shown in Table 2, resulting from atypical cortisol secretion and/or abnormal signal transduction [47, 81–84]. Generally, low levels of glucocorticoids are associated with more severe inflammatory responses due to rising levels of proinflammatory mediators, whereas high levels of glucocorticoids, particularly in the absence of inflammation, leads to increased risk of infections and issues with immunity due to the immunosuppressive properties of glucocorticoids [23].

The chemical structures of glucocorticoids are similar to endogenous compounds but with modifications to enhance therapeutic properties while minimizing adverse effects [29, 31, 85]. Given that the primary action of glucocorticoids is through receptors, there is particular interest in the development of selective glucocorticoid receptor agonists that have minimal mineralocorticoid receptor activity. Mineralocorticoid activity is thought to be associated with many of the transactivating properties that lead to adverse effects, while glucocorticoid receptor activity is thought to be associated with many of the transrepression properties that suppress proinflammatory genes [20, 30, 86]. Unfortunately, the therapeutic effects mediated by glucocorticoid receptors are accompanied by HPA axis suppression. Early glucocorticoids, such as hydrocortisone, have both glucocorticoid and mineralocorticoid activity while more recently developed drugs have less mineralocorticoid activity like

prednisolone and almost no mineralocorticoid activity like dexamethasone [29]. A brief summary of pharmacodynamics for select glucocorticoids are provided in Table 3 (adapted from [75]). In general, the clinical effects of synthetic glucocorticoids are dependent on drug solubility, absorption rate, receptor affinity, metabolic rate, and dose, which vary by drug [87]. Therefore, differences in the pharmacodynamics across this class of drugs must be accompanied by an understanding of pharmacokinetics to optimize the dose-exposure-response relationship as discussed in **Sections** 4.1 **and** 4.2.

4.1 Differences in use and administration routes

When glucocorticoids are administered for health emergencies, high doses are usually given intravenously whereas chronic diseases are managed with low oral doses [85]. Any of the glucocorticoids may be administered intravenously or orally depending on the indication and severity of the condition. Similar immunosuppressive and anti-inflammatory properties can be maintained using dose equivalency, enabling clinicians to switch between compounds as needed [88]. It is known that the duration and extent of suppressive effects on the HPA axis are dependent on the length of time systemic concentrations remain above the IC50, which is inherently a function of the dose, clearance, and potency of the drug administered [19]. For example, greater suppression of the HPA axis is usually observed with higher doses due to increased negative feedback signals [53, 89]. Consequently, the choice of one synthetic glucocorticoid over another stems from the nature of the condition being treated, frequency of dosing, and the severity of the condition. Generally, hydrocortisone is considered a short-acting glucocorticoid. Prednisolone and methylprednisolone are recognized as intermediate-acting, while dexamethasone has extended suppressive effects on the HPA axis even after administration of a low single dose [88].

Hydrocortisone is most often used for hormone replacement due to adrenal insufficiency [90, 91]. Considering its structural equivalency to endogenous cortisol, hydrocortisone is the preferred drug due to its dual glucocorticoid and mineralocorticoid activity that matches endogenous cortisol action [89]. Prednisolone and methylprednisolone are commonly used to treat a variety of inflammatory and immune disorders, including rheumatoid arthritis and asthma [92, 93]. When administered for hormone replacement, prednisolone and methylprednisolone must be administered in conjunction with a mineralocorticoid drug to compensate for the reduced mineralocorticoid activity [92]. Prednisolone is amenable to chronic treatment due to its short half-life, and is often administered orally as the prodrug, prednisone [92, 94, 95]. Dexamethasone is used pharmacologically for the treatment of inflammation, allergic and autoimmune disorders, leukemia, nausea, and vomiting, amongst other indications, as well as in diagnostics to probe HPA axis functionality for disease identification, such as Cushing’s syndrome or depression [25, 96, 97]. Dexamethasone is also commonly used to suppress the HPA axis to mimic disease states for analysis of other synthetic glucocorticoids [90, 98, 99]. This drug is rarely used for hormone replacement because it lacks mineralocorticoid activity [97]. Given its association with severe HPA axis suppression, dexamethasone is typically used for short-term treatment in severe, acute conditions [6].

4.2 Absorption and disposition of synthetic glucocorticoids

Synthetic glucocorticoids are lipophilic drugs with the bioavailability of oral dosage forms ranging from 60 to 100% [85]. Glucocorticoids are rapidly absorbed when administered orally, with the maximum concentration typically seen within 1 to 3 hours after administration for immediate release formulations [85]. At higher doses, hydrocortisone is associated with reduced dissolution rates and may be classified as class II of the Biopharmaceutical Classification System (BCS) [100]. Prednisolone is considered a BCS class I drug with both high permeability and solubility [101], whereas the permeability and solubility of prednisone are on the borderline of being considered class I [102]. While highly soluble, methylprednisolone and dexamethasone are associated with high or low permeability depending on the study and are classified as BCS classI or III accordingly [103, 104]. Dexamethasone undergoes hepatic recirculation [85], which may contribute to variability in systemic exposure for this particular drug.

Both hydrocortisone and prednisolone have nonlinear, dose-dependent pharmacokinetics in part due to plasma protein binding, whereas methylprednisolone and dexamethasone typically have linear pharmacokinetics with pharmacological doses [19, 21, 85, 105]. Hydrocortisone and prednisolone bind to both corticosteroid binding globulin and albumin, while methylprednisolone and dexamethasone bind only to albumin [21, 45, 85, 89, 95]. Hydrocortisone and prednisolone will compete with endogenous cortisol for binding sites on corticosteroid binding globulin, affecting the circulating concentrations of unbound endogenous and synthetic glucocorticoids. Within the therapeutic range of prednisolone doses, CBG can become saturated, causing the bound fraction of endogenous cortisol to drop nonlinearly from 95% to 60–70% [95]. Synthetic glucocorticoids are also substrates for 11β-hydroxysteroid dehydrogenase types 1 and 2 [21, 85, 95], which will influence the relative amounts of active and inactive glucocorticoid forms. Similar to the interconversion between cortisol and cortisone, prednisone and prednisolone will undergo interconversion by the 11β-HSD enzyme system. Therefore, compounds like prednisone are considered both a prodrug and a metabolite [21, 95]. The possible activity of 11β-HSD2 in the colon may influence absorption of formulations released late in the gastrointestinal tract [98].

All drugs are eliminated by hepatic metabolism and renal excretion of inactive metabolites as well as some un-metabolized drug [85]. Hydrocortisone and prednisolone have short half-lives, typically less than 3.5 hours with no drug accumulation between doses, even when patients are administered multiple daily doses, making these compounds preferable for chronic treatment with short dosing intervals [89, 94]. Prednisolone clearance is dose-dependent due to plasma protein binding with greater clearance and apparent volume of distribution at higher doses given a higher fraction of unbound drug [101]. The half-life of methylprednisolone is comparable to hydrocortisone and prednisolone with reported values up to 2.5 hours [85]. In contrast, dexamethasone has a much longer half-life of 36 to 72 hours and is typically administered at lower doses because of its potent glucocorticoid receptor activity and longer duration of action [91].

Studies exploring the pharmacokinetics of synthetic glucocorticoids have shown that the number of compartments necessary to describe distribution and elimination vary by drug type, dose, and administration route. This observation highlights the potential complexities

of pharmacokinetics for this drug class and the underlying influences that circulating cortisol has on drug exposure. Prednisolone is often described by a 2-compartment model following intra-venous administration while oral delivery requires a 1 or 2 compartment model depending on dose [85, 106]. Variability in prednisolone pharmacokinetics are likely attributed to saturable processes, such as plasma protein binding or interconversion by the 11β-HSD enzymes, that influence drug distribution to tissues and eventually its elimination from the body, which is at least partially dependent on circulating cortisol levels. Methylprednisolone requires a 2-compartment model following injections of high doses whereas oral or low intra-venous doses are described by 1-compartment. Dexamethasone is typically described by 2-compartment models [88].

5 Case Study: Modeling of synthetic glucocorticoids for dose equivalency evaluation

As discussed in Section 4, several differences exist in the pharmacokinetics and pharmacodynamics of synthetic glucocorticoids, which ultimately influence the magnitude and duration of the biological effects of each drug. Physicians often leverage these differences to optimize patient treatment, requiring an understanding of the equivalent doses needed to produce similar therapeutic effects. This case study demonstrates how models are used to improve our understanding of synthetic glucocorticoid for successful pharmacological intervention. The pharmacokinetics and pharmacodynamics (PKPD) of prednisolone (PNL), methylprednisolone (MPL), dexamethasone (DEX), and hydrocortisone (HC) were described in healthy male subjects using compartment models to describe drug exposure and indirect response models to describe the effects on cortisol secretion [88]. The compartments models for the time-dependent drug concentration are given in Equations 1–6, where k_a is the first-order absorption rate constant, k_{el} is the first-order elimination constant, k_{12} and k_{21} are the rate constants for transfer of drug between tissue and plasma, and k_{out} is the first-order elimination constant of hydrocortisone which is indistinguishable from that of endogenous cortisol. The model for prednisolone considers the free drug due to nonlinear plasma protein binding.

$$\text{Prednisolone Tablet:} \frac{dC_{PNL,GIT}}{dt} = -k_a \cdot C_{PNL,GIT} \quad \text{Eq. 1}$$

$$\frac{dC_{PNL}}{dt} = k_a \cdot C_{PNL,GIT} - k_{el} \cdot C_{PNL} \quad \text{Eq. 2}$$

$$\text{Methylprednisolone IV:} dC_{MPL} = -k_{el} \cdot C_{MPL} \quad \text{Eq. 3}$$

$$\text{Dexamethasone IV:} \frac{dC_{DEX}}{dt} = k_{21} \cdot C_{DEX,tissue} - \left(k_{12} + k_{el}\right) \cdot C_{DEX} \quad \text{Eq. 4}$$

$$\frac{dC_{DEX,tissue}}{dt} = k_{12} \cdot C_{DEX} - k_{21} \cdot C_{DEX,tissue} \quad \text{Eq. 5}$$

$$\text{Hydrocortisone IV:} \frac{dC_{HC}}{dt} = -k_{\text{out}} \cdot C_{HC} \quad \text{Eq. 6}$$

Synthetic glucocorticoids have a suppressive effect on endogenous cortisol secretion (Equations 7–8), characterized by the inhibitory function, $I_C(t)$, where IC_{50} is the drug concentration that achieves 50% inhibition of cortisol secretion and C_{GC} is the time-dependent concentration of the synthetic glucocorticoids determined by the compartment models [88]. Cortisol secretion in this model is described by a periodic, time-dependent production function, $k_{in}(t)$, and cortisol elimination is described by the first-order elimination rate constant, k_{out}. The production function is described by a two-harmonic Fourier series (Equation 9).

$$\frac{dC_{en}}{dt} = k_{in}(t) \cdot I_c(t) - k_{out} \cdot C_{en} \quad \text{Eq. 7}$$

$$I_c(t) = 1 - \frac{C_{GC}}{IC_{50} + C_{GC}} \quad \text{Eq. 8}$$

$$k_{in}(t) = k_{out} \cdot a_0 + \sum_{n=1}^{2} \left[\left(k_{\text{out}} \cdot a_n + \frac{b_n \cdot 2\pi \cdot n}{24} \right) \cdot \cos\left(\frac{2\pi \cdot n \cdot t}{24} \right) + \left(k_{\text{out}} \cdot b_n - \frac{a_n \cdot 2\pi \cdot n}{24} \right) \cdot \sin\left(\frac{2\pi \cdot n \cdot t}{24} \right) \right] \quad \text{Eq. 9}$$

The pharmacokinetic and pharmacodynamic parameters were determined by fitting the model to clinical data and are shown in Table 4. Hydrocortisone and cortisol are indistinguishable and thus a joint PKPD model was used to estimate parameter values. For the other drugs, pharmacokinetic parameters were first estimated and then the pharmacodynamic parameters were determined [88]. The concentration-time profiles for the synthetic glucocorticoids and cortisol before and after a single dose are shown in Figure 3.

The model showed that similar drug response can be achieved by adjusting the dose of each synthetic glucocorticoid considering differences in absorption and drug disposition, as well as the strength and duration of the inhibitory effects [88]. Similar models were applied to study the influence of sex and ethnicity on prednisone PKPD [105], sex differences in methylprednisolone PKPD [107], and the effects of administration time on methylprednisolone PKPD [19]. In these examples, indirect response models were used to

describe the suppressive effects of synthetic glucocorticoids on endogenous cortisol secretion.

6 Importance of chronopharmacology for glucocorticoid treatment

Several advances have been made to optimize drug structure for enhanced specificity of glucocorticoid receptor-mediated actions and reduced mineralocorticoid activity, leading to fewer adverse effects [11, 29, 58]. Despite these improvements, HPA axis disruption remains a major downfall of long-term term treatment. However, chronopharmacology has proven to be a successful approach to maintaining the balance between homeostatic cortisol activity and the therapeutic effects of synthetic glucocorticoids. Drawing from a strong understanding of the natural rhythms of interest, chronopharmacological intervention supports the return to normal activity in the case of altered or absent rhythms, and additionally can lead to reduced adverse effects associated with disrupted rhythmicity [108]. The success of chronopharmacology relies on balancing the circadian rhythmicity of disease manifestation and adverse effects with the desired therapeutic effects [61]. Diurnal oscillations in physiological mechanisms lead to variability in drug efficacy, pharmacokinetics and drug toxicity with regard to administration time [109]. These concepts have proven to be highly beneficial for other drug classes [43, 110–119] and shows great promise in the advancement of long-term glucocorticoid therapies for patients with inflammatory and immune disorders, and those receiving hormone replacement therapy. Several studies have investigated chronopharmacological therapies that minimize the disruption of endogenous cortisol secretion or mimic the circadian rhythmicity in patients with adrenal insufficiency through careful timing of peak drug exposure with the circadian pattern of various compounds involved in disease activity [19, 21, 98, 120–122].

Importantly, negative feedback to the HPA axis exhibits circadian rhythmicity in normal diurnally active patients [121]. Negative feedback signals are strengthened by drug administration just before the nocturnal rise in ACTH production, resulting in maximum suppression of cortisol secretion, while morning administration has limited influence on HPA axis activity [21, 95]. Additionally, glucocorticoid receptors show diurnal variations in peripheral tissues which could potentiate or negate the local effects of synthetic glucocorticoid dosing [123]. As such, understanding the signal cascades of glucocorticoids in peripheral tissues throughout the day will ensure the desired local activity of synthetic glucocorticoids is achieved. Interestingly, the intrinsic sensitivity of receptors to cortisol is constant throughout the day [19] and so diurnal variations in glucocorticoid activity are attributed to other factors, such as the expression patterns of glucocorticoid receptors or variability in gene transcription susceptible to transrepression or transactivation by glucocorticoids.

Historically, glucocorticoids have been given in the morning for timing with disease symptomology to maximize treatment of allergic, inflammatory, and autoimmune conditions such as asthma, lupus, rheumatoid arthritis or Crohn’s disease [21]. The best example of effective chronopharmacological dosing of synthetic glucocorticoids is associated with the treatment of rheumatoid arthritis. Rheumatoid arthritis is a chronic inflammatory condition in which symptoms are closely linked to the circadian rhythmicity of proinflammatory and

anti-inflammatory mediators, which peak during the evening and day, respectively [24, 121]. Morning administration has been shown to alleviate symptoms by timing drug release with the release of proinflammatory cytokines while also reducing the risk of HPA suppression [121, 124]. Thus, the secretion patterns of cortisol from the adrenal glands are not influenced and cortisol peak concentrations in the morning are still observed as shown in Figure 4 [121]. Although the endogenous cortisol circadian rhythm of rheumatoid arthritis with low or moderate activity remains normal, the natural rhythms can be disturbed when patients have high disease activity [121]. Consequently, any shifts in the endogenous cortisol rhythm due to disease must also factor into selection of an administration time to maintain the lowered risk of HPA suppression.

Rhythmicity in symptom severity is also observed in other conditions. For example, nasal congestion and sneezing associated with allergies tends to be greater in the morning for a majority of patients [43], whereas the risk of an asthma attack is greatest at night [125, 126]. Glucocorticoid receptors mediate diurnal variations in pulmonary inflammatory response which is important during asthma attacks, chronic obstructive pulmonary disease (COPD) exacerbations, and respiratory bacterial infections [127]. Similar to the treatment of rheumatoid arthritis, careful timing of synthetic glucocorticoid administration with the rhythmicity of mediators involved in immune and inflammatory response for these pulmonary indications help to improve symptom relief [128–130]. Patients benefited from prednisone administration at 3:00 PM compared to early morning or late night dosing with improved expiratory volumes [126]. The success of glucocorticoid therapy for the treatment of asthma is dependent on the ability of glucocorticoids to alter transcription of various proinflammatory mediators (interleukins, tumor necrosis factor-α, and chemokines) and anti-inflammatory mediators (inhibitory protein IκB or interleukins Il-1, IL-10, and IL-12) involved in pulmonary immune response [59]. While asthma is considered both an acute and chronic inflammatory disease, timing glucocorticoid administration to maximally suppress proinflammatory mediators which peak at night may help to manage chronic airway inflammation associated with this disease.

Another successful application of chronopharmacology for glucocorticoids is in the management of Addison’s disease through asymmetrical dosing to reduce fatigue and enable realignment of circadian clocks using high doses in the morning and low doses in the afternoon [131]. Patients with autoimmune disorders also benefited from timing drug administration based on diurnal rhythms of the immune system such that evening dosing of prednisolone led to improved treatment [10]. Multiple sclerosis, which is a chronic inflammatory disease affecting the central nervous system, exhibits both seasonal and diurnal variation. Nighttime dosing of intravenous methylprednisolone led to improved symptom reprieve, in terms of rapid onset and greater overall relief, as well as reduced adverse effects, such as restlessness, palpitations, and hot flashes [132]. Further improvement in treatment options for multiple sclerosis may consider seasonal variation in immunity, owing to differences in the basal HPA axis activity throughout the year [133]. While not the emphasis of the current review, this study suggests that patients may further benefit from considering the impact of biological rhythms with periods longer than 24 hours. A similar argument could be made for the influence of the menstrual cycle for women

receiving glucocorticoid therapy due to changes in drug disposition and the role of circulating sex hormones in glucocorticoid activity [105].

6.1 Circadian influence on systemic synthetic glucocorticoid exposure

Another key aspect for successful implementation of chronotherapy is an understanding of how drug exposure varies with administration times. Chronopharmacokinetics considers the natural oscillations of biological processes and functions that influence absorption and disposition, and ultimately the amount of pharmacologically active drug in systemic circulation [134–136]. For orally administered drugs, circadian rhythms in gastric pH, motility and gastric emptying can influence both the extent and rate of absorption throughout the day [43, 137–139]. In general, morning administration of tablets has been associated with faster gastrointestinal transit times in comparison to evening dosing [140]. Moreover, drug distribution to bodily tissues is affected by circadian rhythms in biologically processes, such as blood flow and protein binding [43, 139]. Metabolism and elimination are also altered by biological rhythms due to changes in hepatic and renal perfusion, hepatic Phase I and Phase II enzyme expression, glomerular filtration rate, urine excretion rate, urine pH, and electrolyte balances, amongst other factors [43, 137–139].

While the importance of chronopharmacodynamics has been recognized for glucocorticoids, the influence of circadian variation in absorption and drug disposition properties for synthetic glucocorticoids is less clear. There are conflicting findings for circadian variation in prednisolone pharmacokinetics, such as the volume of distribution, half-life, clearance, and unbound fraction, when given at low doses [19]. Some studies suggested that the rate and extent of absorption of prednisolone or prednisone from the gastrointestinal tract were not influencedby administration time [21, 141]. Other studies indicated that morning administration (8 AM) of methylprednisolone and prednisolone led to higher drug exposure due to reduced clearance [19]. Furthermore, the timing of dexamethasone administration was shown to have a weak effect on pharmacokinetics with a slight increase in the absorption rate when administered at 11 PM compared to administration at 8 AM [142]. General knowledge suggests that circadian influences are expected to be more significant for lipophilic drugs [43]; however, further studies are needed to confirm whether this holds true for synthetic glucocorticoids.

Given that only unbound glucocorticoids have pharmacological influence, variations in plasma protein binding throughout the day may have a significant role in the observed dose-exposure-response relationship. This influence arises from the competition between endogenous cortisol and synthetic glucocorticoids for plasma protein binding sites. Thus, the amounts of unbound and bound circulating glucocorticoids depend on the balance between these species as well as the rhythmicity of corticoid binding globulin expression [143]. This consideration is particularly true for compounds like prednisolone and hydrocortisone which compete with endogenous cortisol for plasma protein binding sites. Maximum binding of prednisolone has been reported at midnight and minimum at 8 AM [144]. Interestingly, the extent of prednisolone binding is in antiphase with the circadian rhythm of cortisol.

6.2 Controlled delivery of synthetic glucocorticoids for chronopharmacological intervention

Synchronization of drug concentrations to rhythms in disease or morbidity activity is aided by the use of specialized formulations or drug delivery systems with controlled release profiles [41, 145]. The need for such advancements stems from the fact that optimal drug release may not coincide with optimal administration time for patient compliance [146]. While single doses in the early morning have been the standard of care due to reduced adverse effects and alignment with peak cortisol concentrations, studies have shown that further relief in inflammatory conditions is achieved when drug exposure peaks before the rise of proinflammatory activity and during the rise of endogenous cortisol, which both occur overnight [24]. Given that glucocorticoids typically achieve peak concentrations within a few hours after oral administration, optimal timing of drug exposure with proinflammatory and endogenous cortisol cycles would lead to sleep disruption and lack of compliance due to administration in the middle of the night. As such, a modified release formulation of prednisone was developed for administration at bedtime with drug release delayed by 4 hours after administration (~2 AM), resulting in less disruption of the HPA axis, while still maintaining anti-inflammatory benefits [20, 24]. There were no signs of adrenal insufficiency even after months of treatment using this formulation strategy, greatly improving the safety of chronic administration [147]. The plasma concentration profiles for immediate release and modified-release formulations are given in Figure 5.

Similarly, modified release prednisone improved treatment of nocturnal asthma when administered at bedtime, reducing the likelihood of nighttime awakenings and symptoms. Timing drug release with the nocturnal activation of inflammatory cells involved in nighttime airflow limitation enhanced the safety and efficacy of the treatment for chronic asthma compared to morning administration at 8 AM [128–130]. Another benefit to chronopharmacological dosing of inhaled corticosteroids was reduced disruption of peripheral clocks in lung tissue. Optimizing the frequency and timing of inhaled dexamethasone minimized phase shifts of clock functions in the lungs compared to once-daily or twice-daily inhaled corticosteroids. While emphasis is often placed on suppression of cortisol levels, maintaining the timing of peak cortisol concentration is also important to host functioning. An animal study showed that a phase advance or phase delay was observed when glucocorticoids were administered at lights on and 6 hours after lights off, respectively [148]. In addition to its pharmacological use, dexamethasone is often used as a probe to diagnose conditions related to the HPA axis and to suppress endogenous cortisol activity while studying other glucocorticoids. In these scenarios, dexamethasone is purposely administered at a time when the HPA axis is most susceptible to disruption for complete knockout of cortisol secretion. As such, dexamethasone is usually taken at 11 PM in the form of immediately release tablets as part of the dexamethasone suppression test [25]. This timing optimizes the suppressive effects of dexamethasone on the HPA axis, inhibiting the nocturnal rise in cortisol.

Adrenal insufficiency often requires lifetime treatment for hormone replacements [91]. As such, it is especially important to develop replacement regimens that successfully replicate diurnal secretory patterns and physiological concentrations [90], while simultaneously

minimizing adverse effects associated with chronic use. Patients receiving hormone replacement therapy benefit from using the smallest dose possible to minimize the likelihood of adrenal crisis while maintaining efforts to replicate physiological rhythms [149]. To manage adrenal hyperplasia, glucocorticoids may be administered in the evening or early night hours to induce production of endogenous cortisol [121]. The normal nocturnal rise in concentration has been successfully replicated using modified release formulations when administered at bedtime and released overnight [98]. Previously, patients with adrenal insufficiency were treated using immediate release hydrocortisone given 2 to 3 times daily at a fixed dose or body weight/surface area adjusted dose [98]. Dose splitting throughout the day was associated with an increased risk of suppression [150]. Replicating the complete diurnal rhythm of endogenous cortisol is not feasible with immediate release formulations [11], even with multiple daily doses, and so hormone replacement therapies have turned towards tailored formulation strategies.

The patterns of cortisol secretion have been better matched using continuous infusions which effectively mimicked the circadian rhythmicity of cortisol secretion but were not practical for patient use [11, 14, 151, 152]. Therefore, modified release, including delayed and sustained, oral formulations have been particularly useful for hormone replacement therapy to control the release of drug into systemic circulation to better match the endogenous cortisol secretion rate. Cortisol profiles following conventional and modified-release oral replacement therapy as well as circadian infusions of hydrocortisone are given in Figure 6.

Furthermore, once-daily delayed release hydrocortisone given in the morning upon wakening significantly reduced adverse effects on the cardiovascular system, glucose metabolism, and quality of life. Weight gain, impaired metabolism, and the frequency of infections were also reversed by switching to the modified release formulation [153]. The improvement in safety was attributed to the absence of the afternoon peak typically associated with other treatment options. Additionally, a modified release glucocorticoid with pH-dependent dissolution along the gastrointestinal tract was shown to have less adverse effects and comparable effectiveness to prednisolone for the treatment of Crohn’s disease [154].

6.3 Monitoring Glucocorticoid Activity

Irregularities in cortisol levels and diurnal rhythms outside the normal physiological range following treatment with synthetic glucocorticoids can be detected by direct measurement of plasma cortisol. Cushing’s syndrome, which is characterized by supraphysiological cortisol levels, is typically diagnosed by measuring the 24-hour free cortisol and late-night salivary cortisol levels (after 10 PM) [155]. Conversely, first morning cortisol measurements (prior to 8 AM) may be used to assess patient risk of adrenal suppression to determine whether the nocturnal rise in cortisol levels is observed following treatment [6]. Serum cortisol, urinary-free cortisol levels or salivary cortisol measurements have been used to determine whether therapy is successful in patients receiving hormone replacement [152]. While salivary cortisol is a measure of unbound biologically active cortisol, serum cortisol is a measure of the total (bound and unbound) circulating cortisol [96]. Saturation of CBG can skew results

for the urinary-free cortisol test, whereas the downside of salivary measurements is the wide inter-individual variability and lack of a correlation to plasma measurements in patients with adrenal insufficiency [152]. Peak cortisol concentration, the time of the peak, and 24-hour cortisol exposure (area-under-the-curve of the cortisol profile) serve as metrics to assess whether the circadian features of the cortisol rhythm have been successfully replicated. Together, these parameters evaluate maximum and cumulative cortisol exposure, along with circadian timing, to ensure the effectiveness and safety of replacement therapy [156].

Furthermore, there are tests to probe the integrity of the HPA axis including the ACTH stimulation test and dexamethasone suppression test. To confirm adrenal insufficiency, the low-dose ACTH stimulation test may be used to detect abnormal cortisol secretion which involves measuring the adrenal response following a bolus injecting of corticotropin [6]. Similarly, the dexamethasone suppression test is used to evaluate the integrity of the HPA axis and degree of suppression following administration of dexamethasone [96]. Atypical results for these diagnostic tests may be indicative of physiological conditions associated with disease states or as a result of long-term use of synthetic glucocorticoids which alters glucocorticoid activity both locally and systemically.

7 Case Study: Modeling chronopharmacological administration of synthetic glucocorticoids using a semi-mechanistic PKPD model

Controlled delivery of synthetic glucocorticoids through chronopharmacological intervention were shown to successfully minimize disruption of endogenous cortisol activity (Section 6), demonstrating how administration time, formulation, and route of administration can be leveraged to achieve the desired biological effects. While many of the aforementioned examples discuss cortisol suppression, fewer clinical results emphasize chronic use and the counterintuitive influences of treatment on the HPA axis activity that can lead to increased cortisol levels. Interestingly, one study found that modified-release prednisone administered at bedtime in rheumatoid arthritis patients resulted in a rise in cortisol levels after 2 weeks of treatment [120]. To further explore the adaptability and responsiveness of the HPA axis following long term synthetic glucocorticoid dosing, a semi-mechanistic model was developed that simulates the diurnal rhythm of endogenous cortisol in the absence of inflammation [157]. This model considers the time-varying feedforward (stimulatory) and feedback (suppressive) processes of the HPA axis. The model describes the secretion of cortisol (CORT) and its precursors ACTH and CRH using nonlinear differential equations with a Goodwin oscillator modified to consider Michaelis-Menten degradation kinetics (Equations 10–12). The model accounts for receptor binding of both synthetic glucocorticoids (GC) and endogenous cortisol (GC_{bound}, Equation 13), and the subsequent pharmacodynamics of the bound receptor complex translocated to the nucleus ($GC_{bound}(N)$, Equation 14), such as negative feedback to the hypothalamus and pituitary gland. Select components of the model are given in Equations 10 to 14 with the complete model provided in Rao et al. [157], where k_{p1} is the zero-order CRH synthesis rate constant; k_{p2} and k_{p3} are the first-order rate constants for ACTH and CORT synthesis; K_{p1} and K_{p2} are the Michaelis-Menten constants for glucocorticoid-induced CRH and ACTH inhibition; V_{d1}, V_{d2} and V_{d3} are the zero-order rate constants for CRH, ACTH and CORT degradation;

K_{d1}, K_{d2}, and K_{d3} are the Michaelis-Menten constants for CRH, ACTH and CORT degradation; k_{on} is the second-order rate constant for glucocorticoid-receptor binding; k_t is the translocation rate constant of the glucocorticoid-receptor complex from cytoplasm to nucleus; r_f is the recycle fraction of the glucocorticoid-receptor complex from nucleus to cytoplasm; and k_{re} is the recycle rate constant of the glucocorticoid-receptor complex from nucleus to cytoplasm.

$$\frac{dCRH}{dt} = \frac{k_{p1} \cdot K_{p1}}{K_{p1} + GR_{bound}(N)} - V_{d1} \cdot \frac{CRH \cdot \left(1 - \frac{light_{effect}}{1 + light_{effect}}\right)}{K_{d1} + CRH} \quad \text{Eq. 10}$$

$$\frac{dACTH}{dt} = \frac{k_{p2} \cdot K_{p2} CRH}{K_{p2} + GR_{\text{bound}}(N)} - V_{d2} \cdot \frac{ACTH}{K_{d2} + ACTH} \quad \text{Eq. 11}$$

$$\frac{dCORT}{dt} = k_{p3} \cdot ACTH - V_{d3} \cdot \frac{CORT}{K_{d3} + CORT} \quad \text{Eq. 12}$$

$$\frac{dGR_{bound}}{dt} = k_{on} \cdot (CORT + GC) \,.\, GR - k_T \,.\, \text{GR}_{\text{bound}} \quad \text{Eq. 13}$$

$$\frac{dGR_{bound}(N)}{dt} = k_T \,.\, GR_{bound} - r_f \,.\, k_{re} \,.\, GR_{bound}(N) \quad \text{Eq. 14}$$

The semi-mechanistic HPA axis model was integrated with compartment models to describe the pharmacokinetics of a once-daily dose of a synthetic glucocorticoid administered by bolus injection and orally as an immediate release or extended release formulation [157]. The concentration-time profiles for drug exposure and the nominal cortisol rhythm are shown in Figure 7A and B, respectively. The change in amplitude and phase of the modified cortisol rhythm are shown in Figure 7C and D following a single daily dose. These simulations reveal alteration of the rhythmic characteristics of endogenous cortisol are highly dependent on the administration time of the once-daily dose, yet normal activity can be preserved by carefully timing drug administration based on the formulation characteristics [157]. The study suggests that formulation properties can be systematically manipulated to optimize dosing time and the extent of cortisol suppression or induction to achieve the desired pharmacodynamic effect. Furthermore, the model reveals the nontrivial influences of synthetic glucocorticoids on HPA axis activity (i.e. induction) that are otherwise not captured by simpler models. Finally, the studies supported by this model-based approach emphasized the need to use multiple metrics (amplitude, phase, 24-hour AUC) to comprehensively study alterations in the diurnal rhythms in response to chronopharmacological intervention [157].

8 Reducing patient risk through chronopharmacological dosing

Considering that glucocorticoids have pleiotropic effects, leveraging knowledge of the pathways involved in both therapeutic and adverse effects of systemic glucocorticoids will further the development of effective and safe treatments. The acrophase (time of peak concentration) for various physiological functions relative to the rest-activity cycle in humans is given in Figure 8 [41]. While this list is by no means comprehensive, the schematic highlights how expression of various physiological compounds are distributed throughout the 24-hour day. The benefits of chronopharmacological dosing to minimize HPA axis disruption is generally accepted, but the link between chronopharmacology and other adverse effects is still under study. An example of progress towards this goal is related to the influence of glucocorticoid treatment on glucose levels and insulin secretion. Under normal conditions, endogenous glucocorticoids are responsible for maintaining glucose homeostasis. Elevated glucose levels are observed following both morning and evening doses of hydrocortisone, but reduced hyperglycemic effects were observed when administered in the morning [14, 42]. Similar findings were observed for patients receiving prednisolone to treat COPD [158]. These observations provide evidence that the risk of serious adverse effects, such as treatment-induced diabetes, may be minimized by proper timing of drug administration [6]. Moreover, a common adverse effect of chronic glucocorticoid treatment involves the disruption of normal blood pressure patterns. Glucocorticoids exhibit their influences on the cardiovascular system through angiotensin II receptor signaling which are important modulators of blood pressure [23]. Hypertension and hypotension are associated with supra-physiological and sub-physiological exposure to glucocorticoids, respectively [159]. While the exact mechanisms responsible for glucocorticoid-induced changes in blood pressure are not fully understood, there is evidence that an imbalance between vasoconstriction and vasodilation activity may be important [32]. Thus, reduced cardiovascular effects may be achieved by minimizing the disruption of this balance. Furthermore, glucocorticoid excess leads to drug-induced osteoporosis by transrepression of the genes involved in bone formation. The impact of glucocorticoids on bone and mineral metabolism are both dose and time dependent [160]. Typically, glucocorticoid-induced osteoporosis is treated after its occurrence [160], but chronopharmacological dosing represents a potential approach to prevent adverse effects on the skeletal system by timing dosing with the circadian variation of osteoblast and osteoclast differentiation and turnover [161].

Recently, an ancillary study of the DREAM clinical trial formalized the link between adverse effects and altered gene expression in peripheral tissues [37]. The study showed that adverse effects on the cardiovascular system, glucose metabolism, and quality of life were alleviated when disruption of peripheral clock genes was minimized. The improvement in clinical manifestations was attributed to the resynchronization of endogenous and exogenous zeitgebers, that is, the realignment of peak exposure to exogenous hydrocortisone with peripheral tissue functions.

9 Patient factors affecting chronopharmacokinetics

Due to the inherent variability across patients in pharmacokinetics and crosstalk between the neuroendocrine and immune systems, efforts to establish the relationship between dose and HPA axis suppression has been difficult [147]. Physiological factors, such as chronotype, sex, age, race or disease state, contribute to substantial variability in pharmacokinetics as well as variation in the underlying regulatory mechanisms and responsiveness of the HPA axis [14, 162–167]. This behavior is observed in clinical studies evaluating the duration and extent of cortisol suppression, which is shown to be highly variable across patient subgroups as a result of disease, ethnicity or sex [19, 107, 168]. While cortisol levels tend to reflect long-term individual traits, the responsiveness of the HPA axis to synthetic glucocorticoids appears to be more closely tied to clinical state [168]. Patients suffering from post-traumatic stress disorder (PTSD) at the time of the study exhibited greater cortisol suppression following administration of dexamethasone compared to patients without PTSD regardless of whether these patients were previously exposed to trauma [168]. Furthermore, glucocorticoid activity in peripheral tissues can contribute to inter-individual differences due to variability in the negative feedback on ACTH secretion, 11β-HSD activity, CBG levels, and active transporters, such as P-glycoprotein, which regulate local concentrations of cortisol [77]. Polymorphisms in genes involved in glucocorticoid transport and metabolism contribute significantly to inter-individual variability in the efficacy and toxicity of patients suffering from Crohn’s disease and ulcerative colitis [71]. Body weight and body surface area have been recognized as important determinants of clearance and are routinely accounted for in glucocorticoid replacement therapy [151]. Yet, significant variability in patient exposure and response is still observed. Some patients are susceptible to all adverse effects with low doses of glucocorticoids, while others show minimal side effects at high doses.

Sexual dimorphism in susceptibility to autoimmune and chronic inflammatory disorders has, in part, been attributed to differences in the underlying regulatory mechanisms of the HPA axis across sexes, such as greater adrenal sensitivity and weaker negative feedback in females [163]. Given differential regulatory mechanisms in basal activity of the HPA axis, one would expect differences in the response and activity of the HPA to drug administration. One study reported a greater potency of methylprednisolone in female subjects. However, the increased sensitivity to glucocorticoids was balanced by higher methylprednisolone clearance in females such that same overall therapeutic effect was observed across sexes [85]. Another study reported lower clearance and volume of distribution of free prednisolone in women compared to men, when corrected for body weight, following a single oral dose. Interesting, differences in the pharmacokinetic parameters resulted in similar half-life in women and men [105]. Sex differences in pharmacokinetics of synthetic glucocorticoids vary by drug due to differences in the glucocorticoid and mineralocorticoid receptor activity as well as the displacement of cortisol from plasma protein binding sites when the drug is a substrate of corticoid binding globulin. While sex differences were observed for pharmacokinetics but not the pharmacodynamics of prednisolone, the opposite was true when race was treated as the covariate. The sensitivity of various biomarkers was dependent on race, whereas pharmacokinetic parameters showed no differences. This suggest that

different patient subgroups may be more susceptible to adverse effects due to differences in drug exposure and sensitivity [105].

Another key consideration is the influence that age has on the basal activity of the HPA axis. Diurnal cortisol rhythms change with age, manifesting as phase advances, lower nadirs, and dampened amplitude in elderly compared to young individuals [156]. Inter-individual differences in clock phase may also be clinically relevant and the success of chronopharmacological dosing relies on proper timing of drug exposure with specific physiological functions [169]. Likewise, differences in glucocorticoid receptor sensitivity may contribute significantly to variability in the dose-response relationship, given the critical role that glucocorticoid receptors play in physiological mechanisms of glucocorticoids [152]. Genetic variation in glucocorticoid pathway regulation and activity is a significant factor in inter-individual differences in glucocorticoid treatment [170]. For example, polymorphisms in the glucocorticoid receptor gene are sometimes accompanied by cardiovascular risks such as irregular blood pressure, low glucose, or low total cholesterol, which may partially explain why some patients are at a greater risk for such adverse effects while receiving treatment [35]. Furthermore, the effectiveness of treatment varies with glucocorticoid activity. For example, some patients with inflammatory bowel disease (IBD) require chronic therapy to stay in remission whereas others require treatment during flare-ups [81]. While intrinsic glucocorticoid resistance leads to drug resistance at pharmacological doses [74], glucocorticoids hypersensitivity can actually aid treatment. For example, lower disease activity of IBD, marked by less gut inflammation and improved mucosal healing, was observed in patients with higher glucocorticoid sensitivity and drug-induced adrenal insufficiency, although other side effects, such as osteoporosis and infections, persisted [171]. Successful treatment is likely due to the favorable increase in glucocorticoid activity in the gut, with epithelium integrity, cell-cell adhesion, and mucus hypersecretion modulated by local receptor activity [172]. Interestingly, the same individual can show significant variability in the magnitude and specificity of action across tissues and even across phases of the cell cycle, requiring a deeper understanding of the signal transduction pathways involved in both therapeutic and adverse effects [173]. Variability inherent to the activity of 11β-HSD enzyme system may contribute to an individual's risk of adverse effects associated with chronic over-exposure at the tissue-level. Accounting for such differences could provide another opportunity to tailor replacement therapies for protection against detrimental effects on the cardiovascular system, central nervous system or bone [174].

10 Conclusions

Cortisol rhythm irregularity due to pharmacological intervention or adrenal insufficiency is a major health concern given the critical role of glucocorticoids in an array of metabolic, anti-inflammatory, immunosuppressive, and cognitive processes. Over the last several decades, significant progress has been made towards elucidating the genomic and non-genomic actions of systemic glucocorticoids which have led to the development of drugs with reduced mineralocorticoid activity and improved safety. Yet, HPA axis disruption remains a central concern with chronic high dose administration. Disruption of glucocorticoid-mediated functions can be minimized and potentially eliminated through

chronopharmacological dosing regimens that maintain the potent therapeutic effects for treatment of immune and inflammatory conditions as well as for hormone replacement therapy. To date, several studies have emphasized the potential for chronopharmacological dosing of glucocorticoids to limit HPA axis disturbance or to successfully replicate the diurnal rhythm of cortisol secretion. Relying on the interplay between the HPA axis and the immune system, specialized formulations and drug delivery systems have enabled peak drug exposure to be synchronized to the nocturnal rise in proinflammatory mediators and cortisol. Manipulation of the pharmacological exposure profile to minimize disruption of endogenous cortisol or to support the development of hormone replacement therapies has yet to be fully explored. This potential was demonstrated theoretically using an exploratory model developed by Rao et al., which showed how administration time, dosing strength, and shape of the drug exposure profile could be leveraged to minimize disruption of the endogenous cortisol profile or to supplement endogenous cortisol levels by inducing its production at select administration times [157]. Furthermore, suppression of the HPA axis is dependent on slow and fast signaling cascades proportional to the rate of change in concentration and the absolute concentration of cortisol, respectively [64]. Understanding diurnal variations in these negative feedback cascades represents another understudied aspect of pharmacological intervention.

Therapy is further complicated by CBG and 11β-HSD activity [155]. Plasma protein binding and enzymatic interconversion can influence drug exposure, echoed by differences in the time to maximum concentration (t_{max}) and terminal half-life [53]. While the inhibitory effects of synthetic glucocorticoids on secretion of cortisol are widely accepted, the influence of synthetic glucocorticoids on endogenous cortisol elimination are less clear. Originally, elimination of cortisol was thought to be independent of drug clearance [19]. However, displacement of endogenous cortisol by exogenous cortisol at the binding sites of plasma proteins has potential to influence the elimination of endogenous cortisol. Due to this competitive protein binding, endogenous cortisol elimination may not be entirely independent of drug clearance and vice versa. Therefore, dosing strength and frequency need to be adjusted based on absorption of oral glucocorticoids from the gastrointestinal tract and half-life of cortisol in systemic circulation around the time of dosing [53].

Chronopharmacology benefits from a strengthened understanding of glucocorticoid action to balance beneficial immunosuppressive and anti-inflammatory properties with the risk of systemic disruption of various biological functions, such as blood pressure regulation or glucose homeostasis. Physiological factors, such as chronotype, sex, age, race or disease state, contribute to substantial variability in pharmacokinetics as well as variation in the underlying regulatory mechanisms and responsiveness of the HPA axis, inherently complicating the cross talk between the neuroendocrine and immune systems. Incorporating such patient factors show great promise towards maximizing the therapeutic potential of glucocorticoid therapy with lower doses and overall safer treatment options. The case studies presented in this review highlighted the utility of modeling in glucocorticoid research to support such goals, revealing how counterintuitive and nontrivial behavior of the HPA axis were unveiled using physiologically and semi-mechanistic representations of the HPA axis. Similarly, the use of physiologically-based pharmacokinetic models, rather than simpler compartment models to describe drug exposure, would facilitate the integration of circadian

dynamics and physiological factors that contribute to the significant time-of-day and inter-individual differences in clinical response.

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Abbreviations List

HPA axis	hypothalamic-pituitary-adrenal axis
CRH	Corticotrophin-releasing hormone
ACTH	Adrenocorticotrophic hormone
CBG	Corticoid binding globulin
11β-HSD1	11β-hydroxysteroid dehydrogenase type 1
11β-HSD2	11β-hydroxysteroid dehydrogenase type 2
BCS	Biopharmaceutical Classification System
PGGR	Primary generalized glucocorticoid resistance
PGGH	Primary generalized glucocorticoid hypersensitivity
COPD	Chronic obstructive pulmonary disease
PTSD	Post-traumatic stress disorder

11 References

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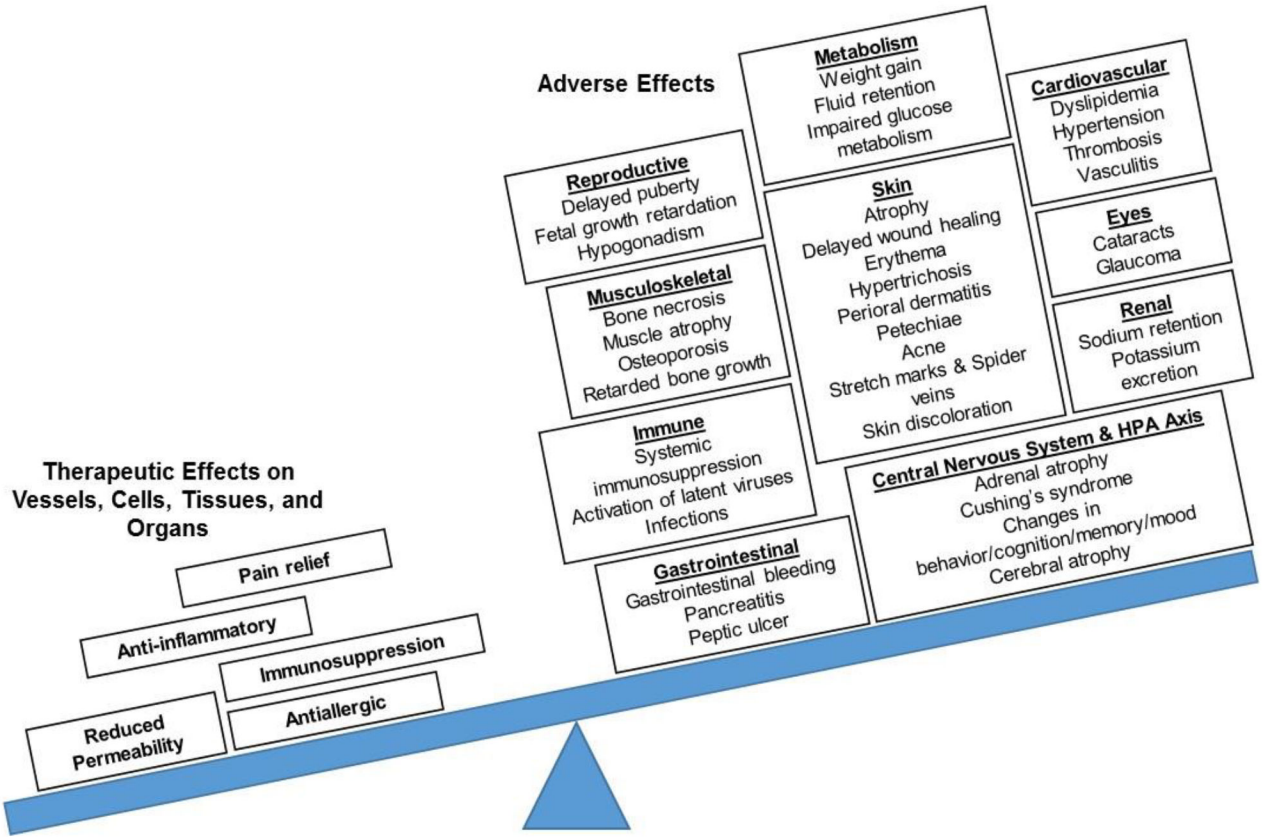

Figure 1:

Therapeutic and adverse effects associated with glucocorticoid therapies. Glucocorticoid treatment is accompanied by several adverse effects across peripheral tissues and many biological processes. For safe and effective treatment, the therapeutic benefits of synthetic glucocorticoid administration must outweigh the risk of these adverse effects. Figure adapted from Liu et al. [6] and Buttgereit et al. [30].

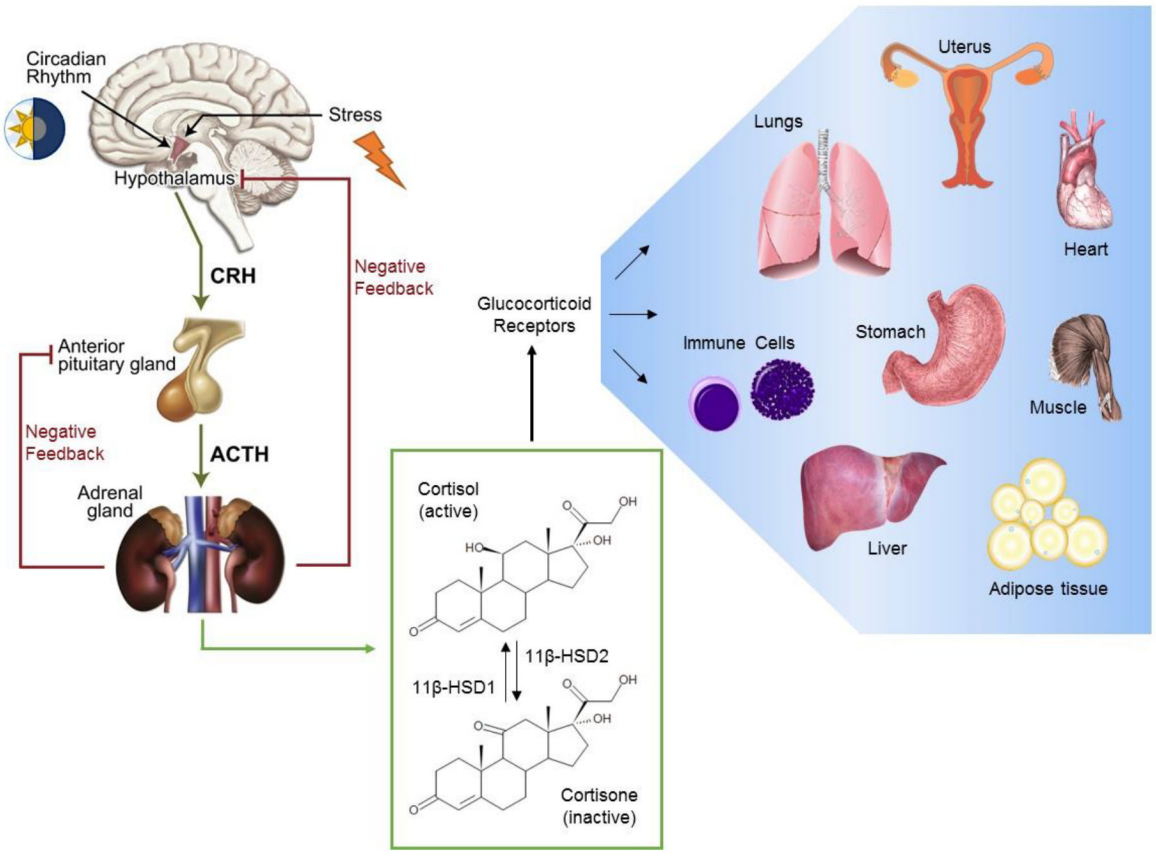

Figure 2:

Systemic and tissue-level regulation of glucocorticoids. Glucocorticoid synthesis is regulated by the hypothalamic-pituitary-adrenal (HPA) axis, comprised of stimulatory and negative feedback signals which control the secretion of corticotrophin-releasing hormone (CRH) from the hypothalamus, adrenocorticotrophic hormone (ACTH) from the pituitary gland and finally cortisol from the adrenal glands. The 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme system is responsible for the activation and deactivation of cortisol, which in part is responsible for local regulation of cortisol. Cortisol induces its pleiotropic influences on peripheral tissues through glucocorticoid receptor-mediated actions, supporting the normal physiology and functioning of these organ systems. Figure adapted from Cruz-Tropete et al. [34, 51] and Oakley et al. [52].

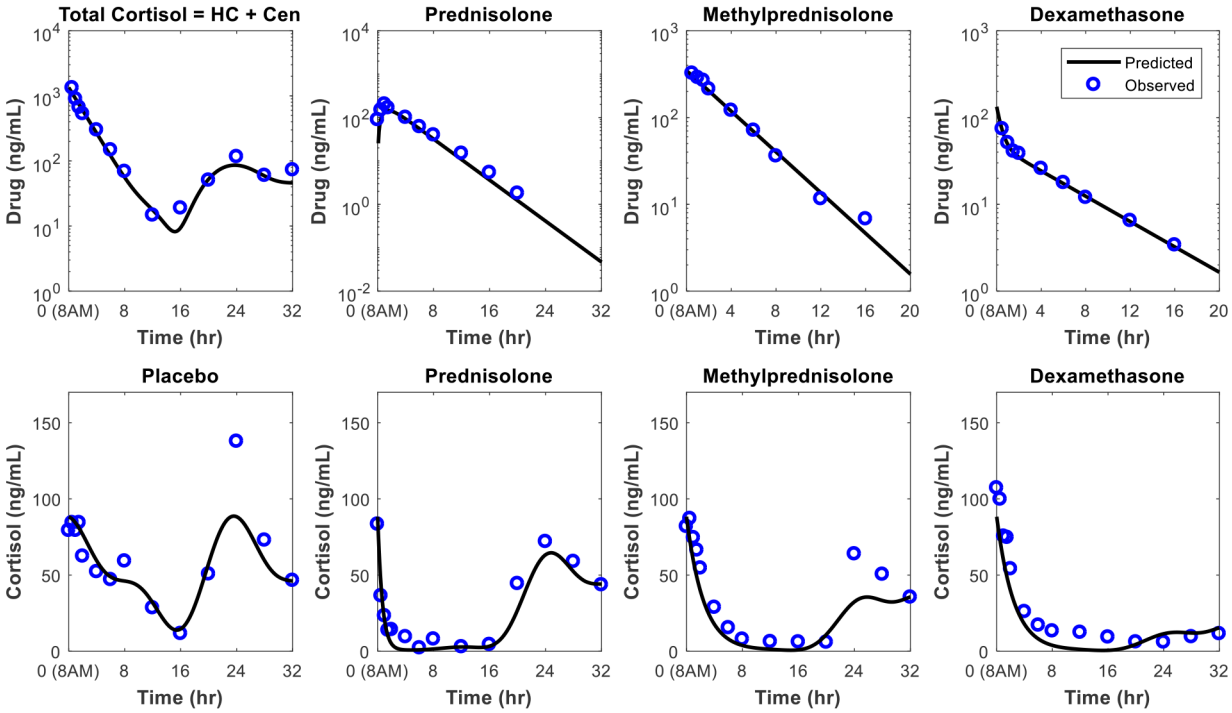

Figure 3:

Concentration-time profiles for synthetic glucocorticoids and endogenous cortisol. The plasma concentration profiles after administration of a single dose at 8 AM are shown for a hydrocortisone injection, prednisolone tablet, methylprednisolone injection, and dexamethasone injection. The cortisol profiles for the baseline (placebo) and after treatment with prednisolone, methylprednisolone, or dexamethasone are given. Because endogenous cortisol and hydrocortisone are indistinguishable in the biochemical assay used for this study, the total cortisol level following dosing with hydrocortisone is shown. Figure drawn using data from D.E. Mager, S.X. Lin, R.A. Blum, C.D. Lates, W.J. Jusko, Dose equivalency evaluation of major corticosteroids: Pharmacokinetics and cell trafficking and cortisol dynamics, Journal of Clinical Pharmacology, 43 (2003) 1216–1227.

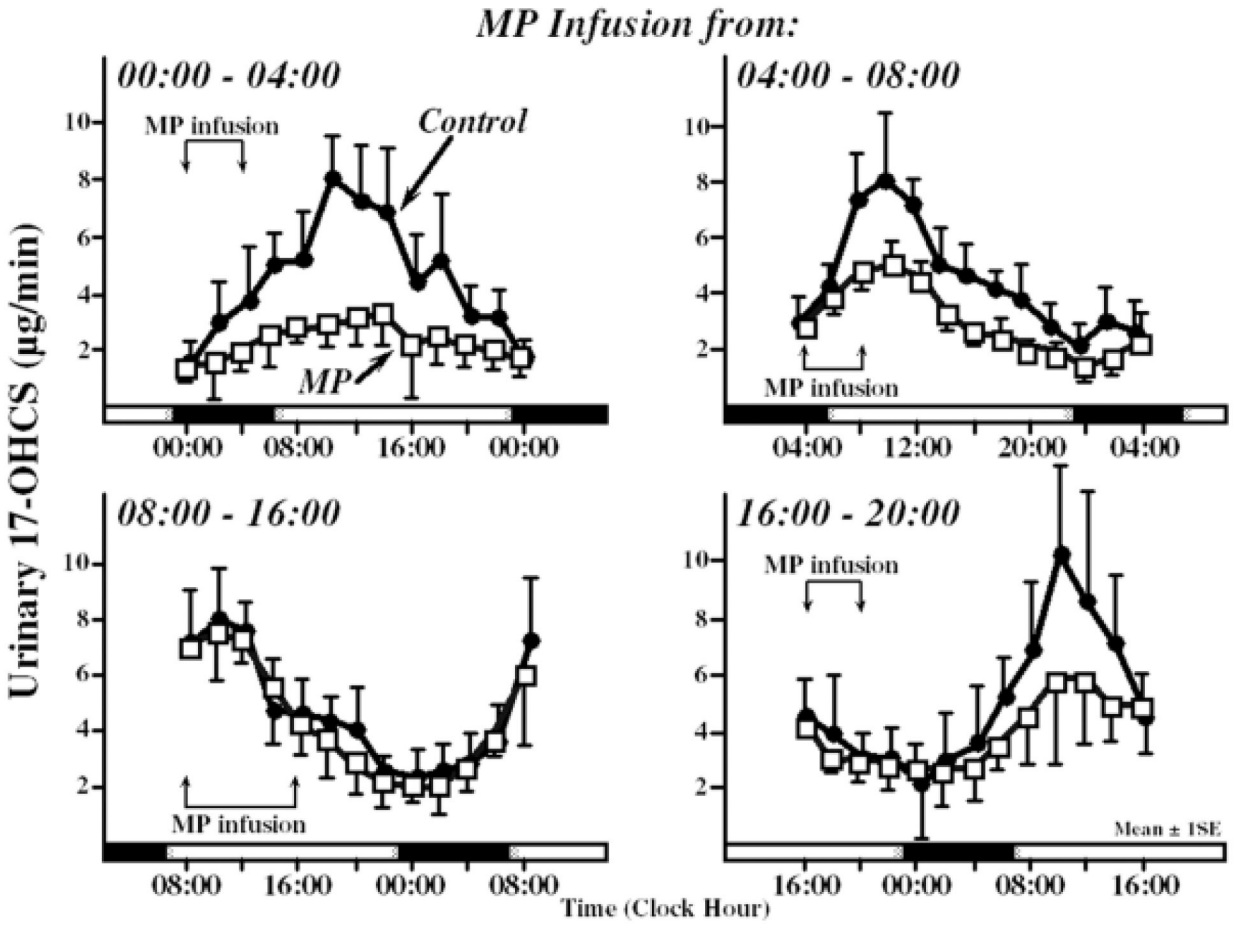

Figure 4:

Time-dependent differences in adrenal suppression following methylprednisolone infusions. The time-concentration profiles of 17-OHCS, a metabolite of cortisol excreted in urine, are shown following 4-hour methylprednisolone infusions for the following time windows: 00:00 to 04:00, 04:00 to 08:00, 08:00 to 16:00, and 16:00 to 20:00. Solid circles represent the control (no drug infusion) and open squares represent the drug-modified cortisol rhythm. Figure drawn using data from Angeli A. Circadian ACTH-adrenal rhythm in man. Chronobiologia. 1974 Sep;1 Suppl 1:253–68. Reprinted from: Haus E, Sackett-Lundeen L, Smoilensky MH. Rheumatoid arthritis: circadian rhythms in disease activity, signs and symptoms, and rationale for chronotherapy with corticosteroids and other medications. Bull Hosp Jt Dis. 2012;70(Suppl 1):S3–10. With permission.

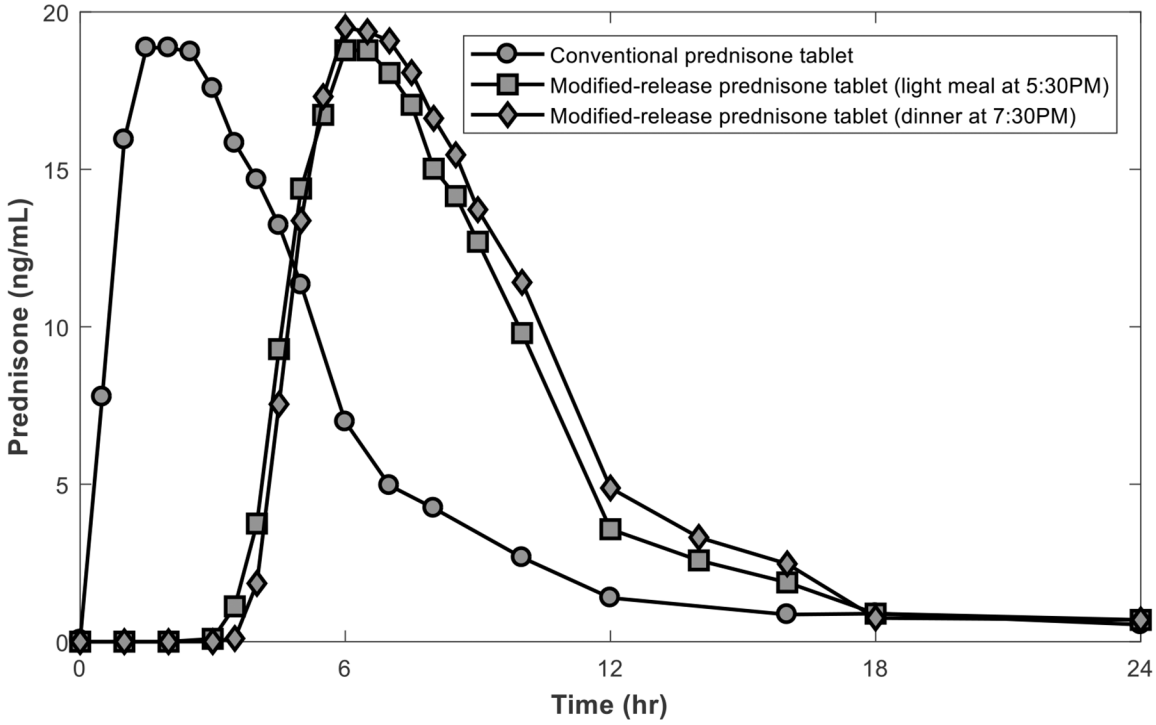

Figure 5:

Plasma concentration profiles for conventional prednisone and modified-release prednisone tablets. The time-concentration profiles of a conventional immediate release prednisone tablet (administered at 2 AM) and modified-release prednisone tablets (administered at 8 PM) after a light meal at 5:30 PM or dinner at 7:30 PM are provided. Figure drawn using data from S.P. Beltrametti, A. Ianniello, C. Ricci, Chronotherapy with low-dose modified-release prednisone for the management of rheumatoid arthritis: a review, Ther Clin Risk Manag, 12 (2016) 1763–1776.

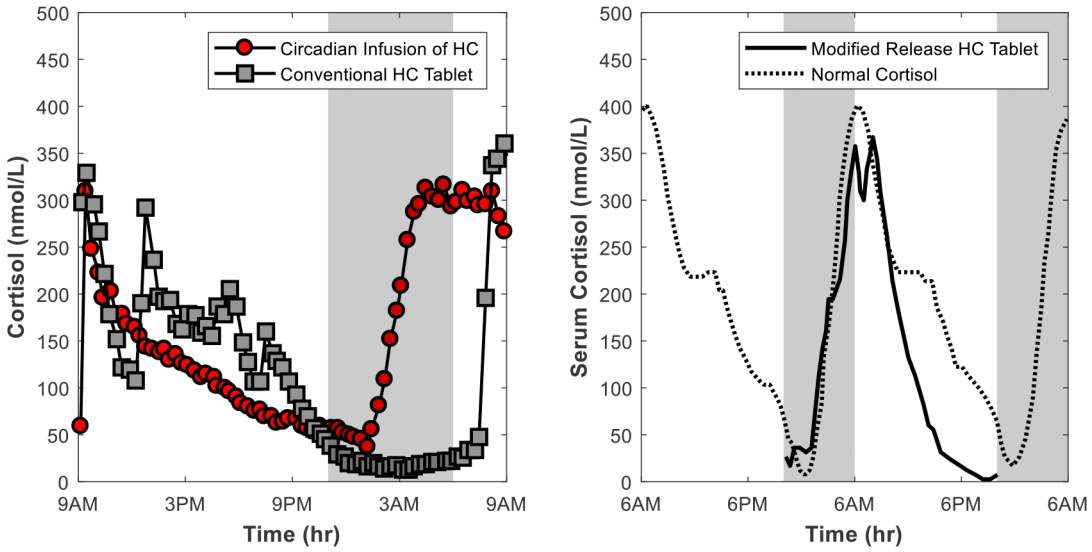

Figure 6:

Concentration-time profiles for cortisol replacement studies. The left panel shows cortisol profiles following a circadian infusion of hydrocortisone (HC) via a pump and administration of a conventional hydrocortisone tablet in patients with Addison's disease and congenital adrenal hyperplasia. The right panel shows the cortisol profiles following administration of a modified release hydrocortisone tablet at 10PM in healthy individuals with suppression of endogenous cortisol by dexamethasone. Figure drawn using data from M. Debono, R.J. Ross, J. Newell-Price, Inadequacies of glucocorticoid replacement and improvements by physiological circadian therapy, Eur J Endocrinol, 160 (2009) 719–729.

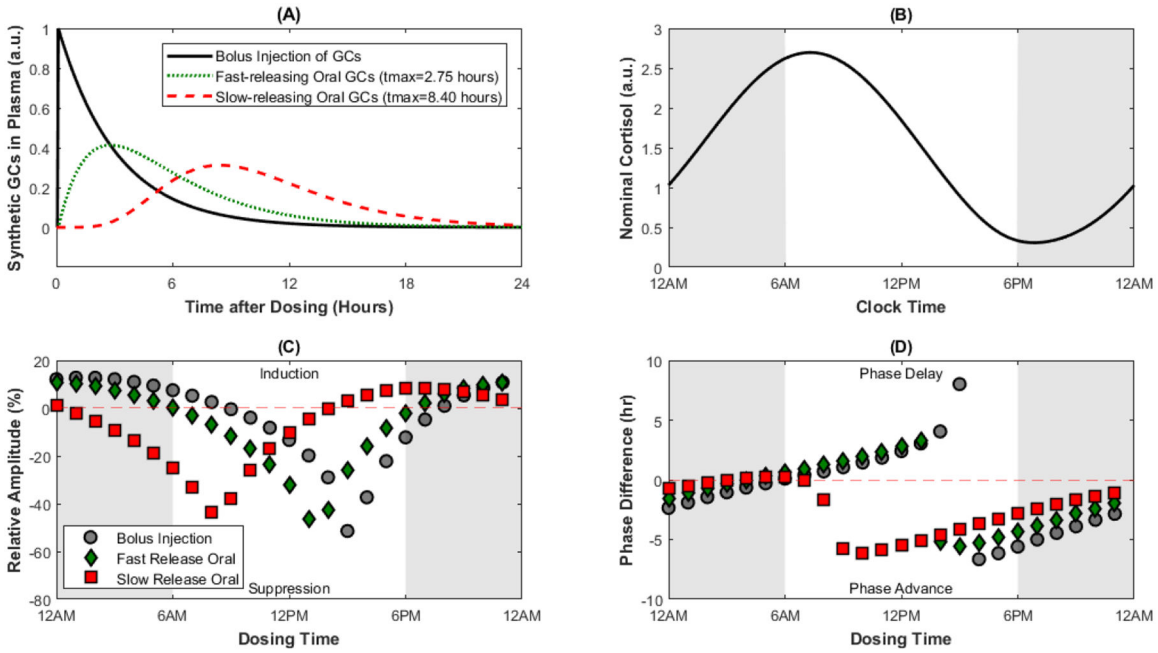

Figure 7:

Modeling chronopharmacological dosing of synthetic glucocorticoids using a physiologically-based HPA axis model. The concentration-time profiles for a bolus injection, fast-releasing oral dose, and a slow-releasing oral dose are given in Panel A. The nominal cortisol profile predicted by the model is given in Panel B. The relative amplitude change (%difference in amplitude before and after once-daily dosing of synthetic glucocorticoids) are given for several dosing times in Panel C, where a positive value indicates induction of the cortisol rhythm and a negative value indicates suppression of the cortisol rhythm. The difference in phase of the cortisol rhythm before and after treatment with synthetic glucocorticoids for several dosing times are given in Panel D, where a positive value indicates delayed timing of the cortisol peak and a negative value indicates an advance in the timing of the cortisol peak. Figure drawn using data from R.T. Rao, M.L. Scherholz, I.P. Androulakis, Modeling the influence of chronopharmacological administration of synthetic glucocorticoids on the hypothalamic-pituitary-adrenal axis, Chronobiol Int, (2018) 1–18.

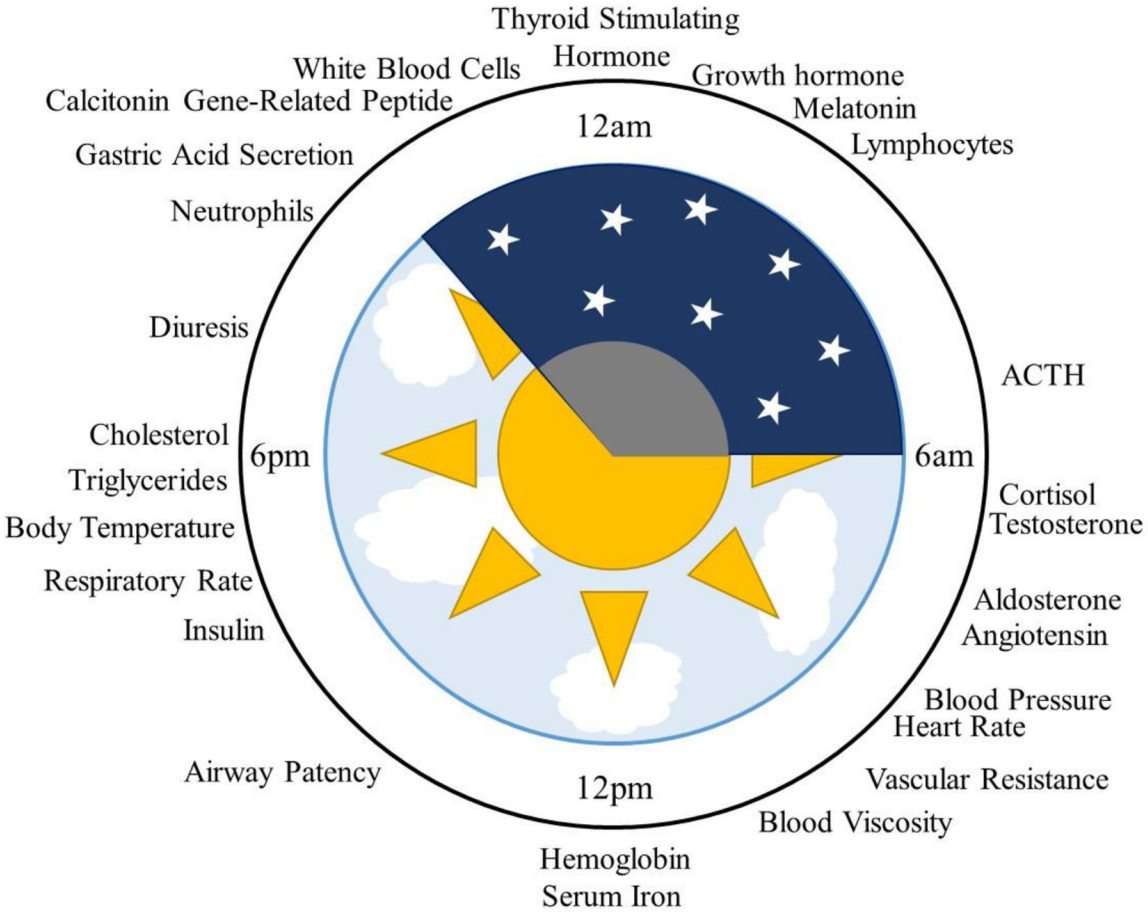

Figure 8:

Circadian rhythmicity of physiological functions in humans. The peak time or acrophase of several biological processes in humans are shown relative to the sleep-wake cycle, indicating distribution of biological processes across the 24-hour day under normal physiology. Figure adapted from Smolensky et al. [41].

Table 1:

Conditions associated with altered activity of the hypothalamic-pituitary-adrenal (HPA) axis

Increased HPA axis activity	**Decreased HPA axis activity**
Chronic stress	Adrenal insufficiency
Melancholic depression	Atypical/seasonal depression
Anorexia nervosa	Chronic fatigue syndrome
Malnutrition	Fibromyalgia
Obsessive-compulsive and panic disorders	Hypothyroidism
Excessive exercise	Nicotine withdrawal
Chronic active alcoholism	Post discontinuation of glucocorticoid therapy
Alcohol and narcotic withdrawal	Cured Cushing’s syndrome
Diabetes mellitus	Premenstrual tension syndrome
Truncal obesity	Postpartum period
Childhood sexual abuse	Following chronic stress
Psychosocial short stature	Rheumatoid arthritis
Attachment disorder of infancy	Perimenopause
“Functional” gastrointestinal disease	
Hyperthyroidism	
Cushing’s syndrome	
Pregnancy (last trimester)	

Note: Table is adapted from Charmandari et al. [47].

Table 2:

Clinical manifestations associated with tissue-specific glucocorticoid excess or deficiency

Affected Tissue	Excess Glucocorticoid Activity	Deficient Glucocorticoid Activity
Central nervous system	Insomnia, anxiety, depression, defective cognition	Fatigue, somnolence, malaise, defective cognition
Liver	Increased gluconeogenesis, increased lipogenesis	Hypoglycemia, resistance to diabetes mellitus
Fat	Visceral fat accumulation	Loss body weight, resistance to weight gain
Blood Vessels	Hypertension	Hypotension
Bone	Stunted growth, osteoporosis	
Inflammation/immunity	Immunomodulation, anti-inflammation, susceptibility to infections and tumors	Increased Inflammation, autoimmunity, and allergy

Table 3:

Pharmacodynamics of select synthetic glucocorticoids

Synthetic Glucocorticoids	Dose (mg)	Anti-inflammatory Activity (relative to hydrocortisone)	Mineralocorticoid Activity (relative to hydrocortisone)	Biological Half-life (hours)
Hydrocortisone	20	1	1	8–12
Prednisone/Prednisolone	5	4	0.3	12–36
Methylprednisolone	4	5	0.5	12–36
Dexamethasone	0.75	30	0	36–72

Note: Table contains data from R.M. Paragliola, G. Papi, A. Pontecorvi, S.M. Corsello, Treatment with Synthetic Glucocorticoids and the Hypothalamus-Pituitary-Adrenal Axis, Int J Mol Sci, 18 (2017).

Table 4:

Estimated Pharmacokinetic and Pharmacodynamic Parameters

Model	Parameter	Hydrocortisone	Free Prednisolone	Methylprednisolone	Dexamethasone
Pharmacokinetics	Dose (mg)	149	37	29	5.7
	k_{12} (h^{-1})	NA	NA	NA	1.11 (39)
	k_{21} (h^{-1})	NA	NA	NA	0.919 (13)
	k_a (h^{-1})	NA	1.25 (21)	NA	NA
	k_{el} (h^{-1})	0.405 (9.4)	0.272 (4.8)	0.27 (4.2)	0.416 (20)
	V/F (L)[a]	119 (15)	168 (9.9)	83.4 (8.1)	42.8 (22)
	CL/F (L/h)[a]	48.2	45.7	22.5	17.8
Pharmacodynamics	IC_{50} (ng/mL)	8.01 (70)	1.25 (14)	0.52 (37)	0.172 (30)
	k_{out} (h^{-1})	0.405 (9.4)	1.54 (26)	0.405[b]	0.405[b]
	AUEC (ng·h/mL)[c]	1070 (230)	1510 (452)	1150 (394)	1430 (237)
	Duration of Suppression (hr)	~15	~15	~28	~32

Data reported as estimate and percent coefficient of variance unless noted. NA = Not applicable; k_{12}, k_{21} = first-order rate constants of drug transport between central and peripheral compartments; k_a = first-order absorption rate constant; k_{el} = first-order elimination rate constant; V/F = volume of distribution corrected for bioavailability; CL/F = total system clearance corrected for bioavailability; IC_{50} = drug concentration leading to 50% suppression of cortisol secretion; k_{out} = first order rate constant of cortisol elimination; AUEC =area under effect curve from 0 to 20 hours ($|AUEC_{baseline} - AUEC_{treatment}|$). Table contains data from D.E. Mager, S.X. Lin, R.A. Blum, C.D. Lates, W.J. Jusko, Dose equivalency evaluation of major corticosteroids: Pharmacokinetics and cell trafficking and cortisol dynamics, Journal of Clinical Pharmacology, 43 (2003) 1216–1227.

[a] F=1 for intravenous hydrocortisone, methylprednisolone, and dexamethasone

[b] Fixed values.

[c] Data in parentheses corresponds to standard deviation.