

HYDROCORTISONE: A TIMELESS MILESTONE IN CLINICAL THERAPY

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ABSTRACT

First isolated in 1949 and introduced into clinical practice in the early 1950s, hydrocortisone revolutionized the treatment of inflammatory and endocrine disorders. Despite the development of more potent and longer-acting glucocorticoids, it remains indispensable in modern medicine.

This review explores hydrocortisone's enduring relevance by examining its pharmacokinetic properties, therapeutic indications, and versatility across clinical contexts. The favorable safety profile of hydrocortisone and its predictable pharmacokinetics allow its practice for both topical and systemic administration. Topical formulations are widely used for mild to moderate inflammatory skin conditions, while localized injections deliver targeted relief in joint and soft-tissue disorders. Systemic regimens, ranging from physiological replacement to high-dose medication, address endocrine deficiencies, acute crises, and severe inflammatory flares. This review summarizes clinical evidence on the safety and efficacy of hydrocortisone across a broad spectrum of conditions, reinforcing its role as a reliable and versatile glucocorticoid in modern medicine.

KEYWORDS

Clinical practice, glucocorticoid, hydrocortisone, inflammation, pharmacokinetics

INTRODUCTION

Glucocorticoids (GCs) are a group of cholesterol-derived hormones essential for the daily functioning of numerous physiological processes. They are secreted by the adrenal glands and regulated by the hypothalamic pituitary adrenal (HPA) axis in a circadian manner and in response to stress. In the 1940s, the collaborative work of Philip Hench,

a rheumatologist, and Edward C. Kendall, a chemist, both at the Mayo Clinic, culminated in the discovery and clinical introduction of a new class of therapeutic agents: glucocorticoids. Since their introduction, glucocorticoids have become a mainstay in the treatment of a wide spectrum of endocrine and non-endocrine disorders, reflecting their essential roles in the regulation of immune

responses, cardiovascular function, growth, water and electrolyte homeostasis, and reproductive physiology^[1,2]. Once secreted in the bloodstream GCs are bound to and transported by plasma proteins which keep the GCs inactive. In the site of action, GCs are released by the activity of several proteases on corticosteroid-binding globulin (CBG). Their lipophilic nature allows the diffusion through the cell membrane and the interaction with their receptor permits their physiological effects. Glucocorticoids inhibit the expression of many genes involved in inflammatory and immune responses^[3]. These include those encoding cytokines, chemokines, cell-surface receptors, adhesion molecules, tissue factors, degradative proteinases, and enzymes such as cyclooxygenase (COX)-2 and inducible nitric oxide synthase, which produce inflammatory mediators^[4].

The successful use of hydrocortisone (cortisol), the principal glucocorticoid (GC) of the human adrenal cortex in 1948, in the suppression of the clinical manifestations of rheumatoid arthritis, allowed the development of numerous compounds with glucocorticoid activity, remaining nowadays the first line-drugs for several diseases despite the numerous side effects associated with their long-term use^[2]. Therefore, the pleiotropic effects of synthetic glucocorticoids allow their frequent use in clinical practice, covering both inflammatory and autoimmune diseases, playing a crucial role in a wide range of metabolic disorders and cognitive signaling processes. GCs are also commonly prescribed to prevent organ transplant rejection and to treat cancers of the lymphoid system such as leukemias, lymphomas, and myelomas^[4]. The most commonly used systemic glucocorticoids are hydrocortisone, dexamethasone, betamethasone, prednisolone and methylprednisolone. These glucocorticoids have good oral bioavailability and are eliminated mainly by hepatic metabolism and renal excretion of the metabolites.

The aim of this review is to provide a comprehensive overview of hydrocortisone, from its discovery to its current clinical applications. We will explore its chemical structure, pharmacokinetics, pharmacodynamics, and diverse therapeutic uses, with a particular focus on recent developments in formulation and administration. By examining hydrocortisone's unique properties and its role in various medical conditions, we aim to highlight its enduring relevance in modern medicine, despite being one of the earliest discovered glucocorticoids.

Hydrocortisone

During his work at Mayo Clinic as a rheumatologist, Hench observed that patients treated with lactophenin, a medication known to induce jaundice, showed improvements in their rheumatoid arthritis symptoms. This observation led him to hypothesize that the conversion of bilirubin into an unknown chemical compound, which he termed "Substance X," contributed to an improvement in the symptomatology of rheumatoid disease^[5,6]. Additionally,

during his studies, Hench noted that pregnant women affected by rheumatoid arthritis improved symptoms during weeks 30-32 of pregnancy, a period in which levels of corticosteroid increase, postulating the implication of the adrenal cortex in this phenomenon^[2].

At the same time, Edward C. Kendall, a chemist at the Mayo Clinic who had previously gained recognition for the isolation of thyroxine and for discoveries that proved effective in the treatment of thyroid goiter and hypothyroidism, developed a strong interest in compounds derived from the adrenal gland. As a result, from the 1930s through the 1940s, adrenal steroids were intensively investigated by several researchers for their potential therapeutic applications, leading to the successful isolation of cortin from the adrenal cortex. During this period, multiple corticosteroids were identified and designated A-F^[6,7]. Among these investigators, Kendall and his collaborators made a particularly significant contribution with the identification of Compound E, which demonstrated therapeutic effects in Addison's disease and colitis, although its clinical utility remained limited.

In light of the results obtained by Kendall, Hench, who was faced with the lack of improvement in his patients with arthritis, hypothesized that Substance X could be compound E, and approached Kendall about a trial with this compound. The successful improvement in clinical results in all 7 patients was then presented to Mayo Clinic staff in April 1949 and to the American Medical Association in May 1949. As they say, "the rest is history," because Compound E became cortisone^[2,6,8].

Building on their earlier success with Compound E, the collaboration between physician Philip Hench and chemist Edward C. Kendall played a pivotal role in advancing the treatment of inflammatory diseases. In 1950, while Hench was managing a patient with a painful, tender shoulder caused by calcific tendinitis, Kendall, with his associates, had identified a more soluble variant of Compound E, derived from the bovine adrenal cortex, which they named Compound F (hydrocortisone). They elucidated the structural features of both cortisone and hydrocortisone, emphasizing the distinct positioning of the oxygen radical at carbon 11 compared to the hydroxyl radical. This structural difference rendered compound F more effective than compound E, which exhibited increased solubility, making it an ideal candidate for local joint injections.

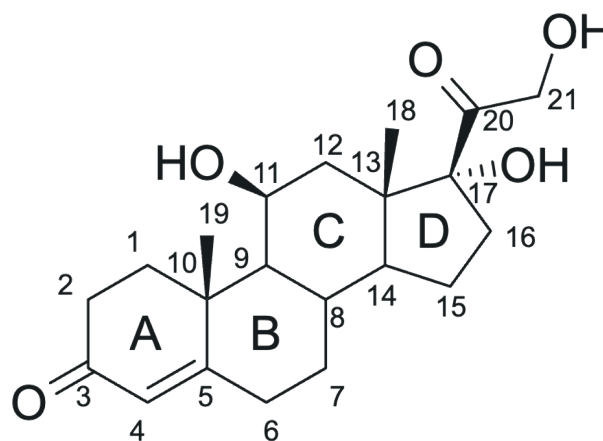
Consequently, Hench proposed the clinical use of compound F, and early trials confirmed its potent anti-inflammatory effects. Following these results, the therapeutic application of both Compound E and Compound F rapidly expanded for the treatment of arthritic joints, with consistent positive outcomes reported by Hench and colleagues. In 1953, Howard et al, after a positive conclusion of a previous trial on compound F, reported the first use of hydrocortisone, both with and without surgery, in the hand and wrist, showing significantly improved patient outcomes^[9,10].

Chemical structure

Hydrocortisone is the synthetic equivalent of cortisol, the endogenous glucocorticoid hormone produced by the adrenal cortex in response to stimulation by adrenocorticotrophic hormone (ACTH). Among the glucocorticoids, hydrocortisone is a naturally occurring compound that lacks synthetic chemical modifications (Fig. 1). It features a pregn-4-ene backbone with hydroxyl groups at positions 11, 17, and 21, and is further substituted with oxo groups at positions 3 and 20. The specific spatial arrangement of these functional groups is crucial in conferring both glucocorticoid and mineralocorticoid activity to the molecule. In particular, the trans conformation of the steroid rings—where all ring junctions are oriented in opposite directions—the presence of an enone system in ring A, and the substitution at C20 with a ketone group, as well as the hydroxyl substitution at C17 (extending from C19), are essential for optimal binding within the glucocorticoid receptor pocket.

Pharmacokinetic

Similar to other corticosteroids, hydrocortisone can be administered in multiple ways depending on its specific clinical application. Consequently, the pharmacokinetics of hydrocortisone, and in particular its absorption, are closely tied to the route of administration. Following oral intake, hydrocortisone is well absorbed, with a nearly complete bioavailability of $96 \pm 22\%$ ^[11], and the maximum concentration (C_{max}) is reached approximately 1.2 hours after administration^[4]. Intravenous injection ensures complete bioavailability and a rapid increase in the plasma concentration of the molecule^[12,13], while intramuscular administration of hydrocortisone may be preferred for a prolonged effect. Additionally, hydrocortisone can be administered locally via inhalation, intra-articular injection, and topical application. Inhaled corticosteroids, including hydrocortisone, undergo a more complex absorption process: 10-20% of the compound reaches the lungs, where it exerts its pharmacological effect, while the remaining 80-90% of the dose typically settles in the oral mucosa. If this portion is not rinsed from the mouth, it may be swallowed and absorbed in the gut, leading to systemic effects^[14,15]. Although hydrocortisone is not commonly used as a modern inhaled corticosteroid, these pharmacokinetic considerations are generally applicable to the class. After topical administration, the absorption of hydrocortisone is closely related to the integrity of the epidermal barrier. Typically, this corticosteroid is used to treat conditions characterized by the loss of skin structure^[16,17]; therefore, after the initial application, it has a higher absorption that decreases after multiple administrations due to the action of hydrocortisone in restoring the barrier^[18,19]. Intra-articular injection allows the molecule to achieve high local bioavailability while limiting systemic absorption and adverse events^[20,21]. Once hydrocortisone reaches the systemic circulation,



| **Figure 1.** Hydrocortisone molecule.

it binds to various plasma proteins; consequently, only about 10% of this corticosteroid is free or unbound in the serum^[22]. The primary proteins that bind hydrocortisone are transcortin, a corticosteroid-binding globulin (CBG), and albumin. Transcortin binds approximately 80% of hydrocortisone with high affinity and low capacity, whereas albumin binds only 10% with low affinity but high capacity^[22–25]. Thus, a dose-dependent increase in free hydrocortisone occurs when transcortin saturates at a concentration higher than 400 $\mu\text{g/l}$ ^[4]. Furthermore, since transcortin is the major protein binding hydrocortisone, it plays a crucial role in regulating free corticosteroids in plasma^[26]. Specifically, the ability of CBG to bind CS may be influenced by various factors, such as genetics, gender, glycosylation sites, concomitant medications, and physiological variations in temperature^[27,28].

The chemical structure of hydrocortisone is identical to that of cortisol; the difference in name serves solely to distinguish the drug from the endogenous product. Therefore, hydrocortisone undergoes the same metabolism as cortisol. The metabolism of corticosteroids is complex and occurs in various tissues; however, the liver remains the primary organ responsible for metabolizing these molecules. hydrocortisone metabolism, like most drugs, follows a two-step process: in phase I, a chemical handle is generated, enabling phase II enzymes to conjugate molecules such as glucuronic acid and sulfuric acid^[29]. The primary phase I enzyme involved in hydrocortisone metabolism is 11- β -hydroxysteroid dehydrogenase (11- β -HSD), which exists in two distinct isoforms: 11- β -HSD1 and 11- β -HSD2. These isoforms catalyze opposing reactions; 11- β -HSD1 primarily facilitates the conversion of cortisone into its active form, cortisol, while 11- β -HSD2 oxidizes cortisol back into cortisone^[30]. Additionally, cortisol and cortisone can undergo further phase I modifications by other enzymes, such as 5- α and 5- β -reductase and 3- α -hydroxysteroid dehydrogenase, resulting in tetrahydro-cortisone, 5b-tetrahydrocortisol, and 5a-tetrahydrocortisol. Furthermore, only in the liver can hydrocortisone be hydroxylated at position 6 to form 6- β -hydroxy-cortisol or converted into 20- β -dihydro-

cortisol by 20- β -oxidoreductase^[31]. In phase II metabolism, the products of phase I are conjugated with glucuronic acid and sulfuric acid by UDP-glucuronosyltransferase (UGT) and sulfotransferase (SULT), resulting in a more soluble molecule that is easier to eliminate^[32,33]. Since hydrocortisone, like cortisol, undergoes extensive metabolism, its half-life is very short, about 1 hour at normal steroid concentrations, whereas it increases to 2 hours in the case of large doses of this drug^[34]. Among all corticosteroids, this short half-life is a unique characteristic of hydrocortisone, as the others exhibit chemical modifications that prevent extensive metabolism^[35,36].

After a rapid metabolization by the liver, hydrocortisone is primarily excreted through urine, as all its metabolites are highly hydrophilic. Furthermore, some studies have highlighted that a variable fraction of corticosteroids (1-20%) is excreted unmetabolized^[4]; this fraction significantly increases in patients with Cushing disease due to their higher plasmatic concentration of cortisol^[37]. Several factors influence the excretion rate of hydrocortisone's metabolites. First, several studies have emphasized that increased fluid intake can enhance urinary-free cortisone excretion^[38-40]. Second, obesity has been associated with a higher cortisol clearance^[41]. In contrast, sodium restriction has been linked to decreases in hydrocortisone elimination^[40]. Lastly, gender has been identified as a factor regulating urinary cortisol excretion, with men exhibiting a greater elimination rate than women^[42,43].

Pharmacodynamic

Hydrocortisone is an anti-inflammatory short-acting glucocorticoid with mineralocorticoid activity that exhibits anti-shock, anti-allergy, and anti-inflammatory action. It raises sugar content in the blood, increases potassium secretion, lowers sodium excretion, possesses anti-metabolic action, and reduces histamine synthesis in the body. Likewise glucocorticoid drugs, hydrocortisone exerts its actions principally via intracellular receptors inhibiting many events of the inflammatory and immune response through the regulation of the transcription of various target genes^[44].

Glucocorticoid receptors (GR) belong to the nuclear receptor superfamily, are widely distributed throughout the body bound to receptor-associated proteins establishing its inactive form. Thanks to its highly lipophilic nature, glucocorticoid molecules, such as hydrocortisone, easily diffuse through the plasma membrane and bind their receptor leading to the formation of the GC-GR complex. This binding leads to a conformational change in the glucocorticoid receptor, which in turn leads to the dissociation of the multiprotein complex, its activation through dimerization, and translocation into the nucleus^[45]. The active form of glucocorticoid receptor uncovers the central site of it, which has more affinity for DNA. Therefore, the interaction with the glucocorticoid response elements (GREs) determines the activation or repression of protein

synthesis, including cytokines, chemokines, inflammatory enzymes, and adhesion molecules^[3,4].

Side effects

It is widely recognized that the side effects of corticosteroids are more common with long-term use than with short-term therapy^[46]. Short-term treatment typically results in reversible adverse effects, including skin reactions, hypokalemia, myopathy, glucose intolerance, hypertension, and immunological issues. Prominent skin manifestations of hypercortisolism include truncal obesity, acne, hyperpigmentation, hirsutism, and petechiae^[47,48]. Additionally, elevated hydrocortisone levels can inhibit fibroblast growth and reduce collagen synthesis, compromising the structural integrity of connective tissue^[49]. On the other hand, elevated cortisol levels contribute to hyperglycemia by directly upregulating genes involved in hepatic carbohydrate metabolism, thereby enhancing gluconeogenesis. The risk of corticosteroid-induced hyperglycemia is further modulated by patient-specific factors, including a family history of diabetes, body mass, age, and the administered steroid dose^[50]. Moreover, short-term therapy may lead to myopathy, which can be acute or chronic. Acute myopathy presents with skeletal muscle weakness and elevated plasma creatine phosphokinase levels, while chronic myopathy shows stable creatine phosphokinase levels. Muscle weakness onset is gradual and usually affects proximal muscles^[51,52]. Since hydrocortisone can bind to the mineralocorticoid receptor, some adverse effects are closely tied to this interaction^[53]. Specifically, hydrocortisone can raise blood pressure in a dose-dependent manner by promoting sodium retention, which in turn increases water retention^[54,55]. Additionally, sodium retention is associated with elevated potassium excretion, leading to hypokalemia^[56].

After long-term therapy, the most common side effects include osteoporosis, ophthalmological effects, adrenal insufficiency, gastrointestinal diseases, and growth suppression. A well-established correlation exists between excessive levels of exogenous corticosteroids and the development of osteopenia^[57,58]; specifically, the administration of hydrocortisone inhibits bone formation by directly affecting osteoblast differentiation and the synthesis of type I collagen. Additionally, it can act indirectly by reducing calcium absorption and increasing its excretion^[59,60]. This results in a loss of bone density that primarily impacts trabecular bones, correlating the use of corticosteroids with a significantly increased risk of bone fractures^[61].

Furthermore, chronic use of hydrocortisone is linked to ophthalmological effects; in particular, glucocorticoids raise the risk of glaucoma by increasing intraocular pressure. This effect typically reverses within four weeks after treatment suspension^[62]. The most prevalent side effect associated with long-term therapy is adrenal insufficiency,

as the administration of exogenous corticosteroids inhibits the pituitary gland's function. A rapid withdrawal therapy can lead to various symptoms such as fatigue, hypotension, and weight loss, and in severe cases, it may result in an adrenal crisis^[38,63,64]. Consequently, scaling the dose gradually at the end of long-term treatment is essential to minimize the risk of adrenal insufficiency. Besides inhibiting adrenal secretion, long-term glucocorticoid therapy also affects growth^[65,66]. Indeed, corticosteroids impact bone formation, nitrogen retention, and collagen synthesis, which are essential processes for anabolism and growth. Furthermore, these substances can inhibit the release of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), two key hormones that regulate growth^[67,68]. Glucocorticoid administration causes the inhibition of NF-κB signaling and other key immunomodulatory transcription factors^[69], leading to an immunosuppressive activity. Importantly, the elevated risk of infection associated with glucocorticoid therapy is attributed to their regulatory influence on immune responses at both the transcriptional and post-translational levels^[70]. Finally, a correlation between corticosteroid intake and the development of peptic ulcers has been noted. However, the data remain controversial, as some studies indicate an association between corticosteroid use and peptic ulcers, while others find no connection at all^[71,72].

Clinical uses

As mentioned above, due to the advantageous safety profile and the physiological pharmacokinetic, Hydrocortisone continues to stand as a cornerstone in clinical practice. Specifically, it retains significance in the

management of both acute and chronic inflammatory conditions, as well as in endocrine disorders, as summarized below in *Table 1*.

Topical uses

Hydrocortisone intended for topical application is formulated as a cream for the treatment of various dermatological conditions. Primarily, it is utilized to manage chronic pruritus, functioning as a first-line therapy for pruritus of inflammatory origin. For optimal efficacy, it is recommended that a 2.5% hydrocortisone cream be applied twice a day; however, for long-term treatment, a two-week interval each month is advised to mitigate potential adverse effects, including skin atrophy and purpura^[73]. Secondly, hydrocortisone is a cornerstone in the treatment of psoriasis since it is well-tolerated and effective in patients with mild symptoms. Corticosteroid treatment can be combined with salicylic acid or other keratolytic agents to better treat plaques with thicker scales since it improves drug penetration^[74,75]. Thirdly, like the other corticosteroids, hydrocortisone is used to treat atopic dermatitis since this class of molecule in numerous RCTs has shown its ability to reduce acute and chronic symptoms of the pathology. Usually, mild-to-high-potency corticosteroids, like triamcinolone and betamethasone, are used to treat acute flares of the pathology; however, for long-term management, the least potent corticosteroid is used to minimize the possible adverse events^[76]. Taken together, these clinical applications explain why hydrocortisone, despite the discovery and the development of newer and more potent agents, remains widely used in the treatment of mild-to-moderate inflammatory skin conditions.

Clinical use	Route of administration	Line of therapy	Clinical notes and therapeutic considerations	References
Chronic pruritus	Topical	First-line	Apply 2.5% hydrocortisone cream twice daily.	[73]
Psoriasis	Topical	First-line	Primarily indicated for patients with mild disease presentations. Combination with keratolytic agents (e.g., salicylic acid) enhances drug penetration in thick plaques.	[75]
Atopic dermatitis	Topical	Second-line	Preferred for long-term treatment over medium-to-high-potency corticosteroids to minimize adverse effects.	[76]
Rheumatoid arthritis	Intramuscular, Intra-articular	Second-line	Used to manage symptoms prior to DMARDs onset; limited to 3–4 administrations per year.	[78,79]
Adrenal insufficiency	Oral	First-line	15–25 mg daily in divided doses (2–3 times/day). Dual-release and slow-release formulations improve patient adherence.	[64,65]
Adrenal crisis	Intramuscular, Intravenous	First-line	100 mg IV/IM bolus, then 200 mg infusion over 24h. Rehydration with 1000 mL isotonic saline is essential.	[90]
Anaphylactic shock	Intravenous	Supportive therapy	Not routinely recommended; may be used in refractory cases or in patients with uncontrolled asthma.	[91]
Inflammatory bowel disease	Oral	First-line	In acute severe ulcerative colitis: 100 mg four times daily until clinical stabilization is achieved.	[97,98]

Table 1. Clinical uses of hydrocortisone, with associated route of administration, therapeutic roles, and relevant clinical considerations.

Local uses

Hydrocortisone, like other corticosteroids, has traditionally been used to alleviate pain and manage rheumatoid arthritis. However, the introduction of disease-modifying anti-rheumatic drugs (DMARDs) has rapidly replaced corticosteroids as the cornerstone of arthritis treatment^[77]. Consequently, current guidelines recommend against the routine use of corticosteroids due to the wide range of side effects associated with long-term therapy. Nevertheless, short-term glucocorticoid treatment (less than three months) remains important for controlling symptoms while awaiting the therapeutic onset of DMARDs^[78]. Although clinical practice now generally favors longer-acting glucocorticoids over hydrocortisone, its shorter half-life may offer a potential advantage by delaying the onset of the adverse effects. Moreover, to minimize adverse effects, hydrocortisone is administered either intra-articularly or intramuscularly, with a maximum frequency of three to four times per year^[79,80]. Thus, hydrocortisone is currently used in specific clinical scenarios where rapid pain relief and symptom control are required.

Systemic uses - adrenal insufficiency

Adrenal insufficiency results from inadequate production of adrenal hormones. Primary adrenal insufficiency (Addison's disease) typically arises from autoimmune destruction of the adrenal cortex, surgical adrenalectomy, or congenital enzymatic defects^[81]. Secondary adrenal insufficiency is commonly caused by hypothalamic-pituitary disorders or chronic glucocorticoid therapy. Glucocorticoid replacement with hydrocortisone remains the mainstay of treatment, with recommended daily doses of 15–25 mg divided into two or three administrations, aligned with the circadian rhythm to minimize metabolic side effects^[82,83]. Newer dual-release and slow-release formulations allow better control of plasmatic hydrocortisone levels since they mimic the endogenous release of cortisol, improving patient compliance^[84,85]. It is crucial to emphasize that patients who chronically take glucocorticoids and undergo surgical procedures should adjust their dosage and the timing of intake during the perioperative period (pre-, intra-, and post-operative). Specifically, in the context of major surgical procedures, an increased dosage is recommended^[86], as well as during other significant physiological stressors such as pregnancy and illness^[87,88].

Hydrocortisone is also the first-line therapy for acute adrenal insufficiency. An adrenal crisis, characterized by a sudden and profound reduction in plasma cortisol levels, typically presents with fatigue, hypotension, abdominal pain, fever, confusion, somnolence, and, in severe cases, coma^[89]. To avert life-threatening complications, guidelines recommend administering an initial 100 mg bolus of hydrocortisone via intramuscular or intravenous injection, followed by a continuous infusion of 200 mg over 24 hours, accompanied by rehydration with 1000 ml of isotonic saline solution^[90]. The uses of hydrocortisone as a lifesaving

therapy in both chronic hormone replacement and the acute management of adrenal crisis highlight its central role in clinical practice due to its pharmacokinetic properties and effectiveness in restoring adequate cortisol levels.

Anaphylactic shock

The use of hydrocortisone in anaphylactic shock remains limited. Current guidelines do not support corticosteroid administration during acute anaphylaxis, as there is insufficient evidence demonstrating their efficacy in preventing prolonged symptoms or biphasic reactions^[91,92]. However, corticosteroids, including hydrocortisone, may be considered in specific clinical contexts, such as anaphylaxis associated with poorly controlled asthma or refractory anaphylaxis, where symptoms persist despite two doses of adrenaline^[93]. In such cases, while hydrocortisone is not part of the initial treatment protocol, it may serve as an adjunctive measure to support recovery. Although not routinely recommended, hydrocortisone still has a crucial supportive role in the management of complex and refractory cases where standard treatments are insufficient. Although the rapid onset of action of systemically administered hydrocortisone can modulate inflammatory pathways, it should not replace adrenaline treatments and is not recommended as an initial treatment for acute allergic reactions.

Inflammatory bowel disease

In the context of inflammatory bowel disease (IBD), particularly in severe exacerbations, hydrocortisone plays a crucial role. IBD encompasses a spectrum of chronic inflammatory conditions of the gastrointestinal tract. Oral corticosteroids are commonly prescribed to control moderate to severe flares; however, in cases where the disease is unresponsive to oral therapy or when surgical intervention is required, intravenous hydrocortisone is administered at equivalent doses until oral therapy can be safely resumed^[94,95]. A subset of ulcerative colitis patients (approximately 15–25%) may develop acute severe ulcerative colitis^[96,97], a life-threatening complication requiring urgent management with intravenous corticosteroids. Clinical guidelines recommend administering 100 mg of hydrocortisone four times daily to induce rapid clinical improvement and stabilize the patient within a few days of the acute episode onset^[98]. The efficacy shown by hydrocortisone in the management of these acute settings makes it a first-line therapy in the treatment of severe IBD manifestations, offering rapid anti-inflammatory effects and contributing to the stabilization of critically ill patients.

CONCLUSION

Hydrocortisone remains a fundamental drug in medicine, despite being one of the first corticosteroids discovered in the 1950s. Its short half-life makes it particularly useful in certain clinical situations, allowing for better control of

therapy and lower toxicity compared to other long-acting corticosteroids.

Hydrocortisone is still widely used topically in the treatment of various dermatological conditions, thanks to its effectiveness and good tolerability. Historically, it has also been employed for intra-articular injections in arthritis, offering a good compromise between efficacy and safety. Although, in current clinical practice, longer-acting corticosteroids are generally preferred due to their prolonged efficacy^[99]. At the systemic level, hydrocortisone is irreplaceable in replacement therapy for adrenal insufficiency and in Addisonian crisis.

Despite advances in formulation and dosing, hydrocortisone therapy still presents challenges, particularly in faithfully replicating the circadian rhythm of endogenous cortisol. However, research continues to refine the use of this historic drug, seeking to maximize its benefits and minimize side effects.

In conclusion, hydrocortisone, while being one of the first corticosteroids discovered, maintains a central role in various therapeutic areas thanks to its unique pharmacokinetic profile and the vast clinical experience accumulated over decades of use. Its versatility and favorable risk-benefit ratio in many indications ensure its prominent place in the modern therapeutic armamentarium^[100].

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