Review Article

The use of local glucocorticosteroids in veterinary practice - An overview

Pul-Luzan Viktoriia[1*], Oliinyk Svitlana[1], Yarnykh Tatyana[1], Rukhmakova Olga[1], Dankevych Oksana[1]

[1]Department of Drug Technology, National University of Pharmacy, Kharkov, Ukraine.

Correspondence: Pul-Luzan Viktoriia, Department of Drug Technology, National University of Pharmacy, Kharkov, Ukraine. pulluzanv@gmail.com

ABSTRACT

The purpose of this review article is to give an overview of the relevance of the use of glucocorticosteroids in veterinary medicines for the treatment of various pathologies in animals, namely cats and dogs. Glucocorticosteroids (GCS) are one of the most commonly used drugs in veterinary medicine, they are powerful anti-inflammatory, and immunosuppressive agents. Corticosteroids are effective in dogs and cats with various diseases: allergic reactions of various etiologies, diseases of the urinary system, ear diseases, various dermatitis. Localglucocorticosteroids (topical corticosteroids (T GCS)) are the main and virtually uncontested drugs for the external treatment of many dermatoses. Due to its anti-inflammatory, antipruritic, immunomodulatory effects, local GCS are the drugs of choice for several diseases in humans and animals. Recently, veterinarians shave identified several skin diseases, the treatment of which is based on drugs with GCS. This group of diseases is called steroid-sensitive dermatoses. It includes diseases that differ in pathogenesis and clinical manifestations, but they are united by the need for a suppressive effect on the cells of the immune system associated with the skin. These are atopic dermatitis (AD), allergic dermatitis, and many others. Modern synthetic corticosteroids have a greater affinity for glucocorticoid receptors, and therefore the effect develops much faster and lasts longer. The article presents glucocorticosteroids, which are most often used in veterinary practice. Two classifications of glucocorticosteroid activity and principles of dosing are presented.

Keywords: Glucocorticosteroids, Atopic dermatitis, Hydrocortisone, Dexamethasone, Prednisolone, Veterinary medicine

Introduction

Glucocorticosteroids (GCS) are steroid hormones that are synthesized by the adrenal cortex. Natural GCS and their synthetic analogs are used both in medicine and in veterinary medicine [1, 2]. The beginning of the glucocorticoid era is associated with the discovery in the mid-1930s of the adrenal cortex hormones, which had anti-inflammatory effects. This was a real revolution in medicine, comparable in importance to the discovery of antibiotics. About 70 years have passed since the Nobel Prize was awarded to Hench, Kendall, and Reichstein for the introduction of GCS hormones into clinical practice [3, 4].

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Viktoriia P, Svitlana O, Tatyana Y, Olga R, Oksana D. The use of local glucocorticosteroids in veterinary practice - An overview. J Adv Pharm Educ Res. 2021;11(2):132-6. https://doi.org/10.51847/lhd43AUMKW

The main and most active glucocorticoid formed in the human body is hydrocortisone (cortisol), others, less active, are represented by cortisone, corticosterone, 11-deoxycortisol, 11-dehydolcorticosterone. The first steroid used in dermatological practice in 1952 was hydrocortisone. In human and veterinary medicine, local glucocorticosteroids (LGCS) are successfully used and today they are the «gold standard» of anti-inflammatory external therapy. GCS have immunological and anti-inflammatory effects on the body of the animal, which explains their frequent use in several diseases that are accompanied by inflammation.

Positive results were obtained from clinical studies about its use in dermatological practice, which later, thanks to the modification of the structure of both the steroid ring of hydrocortisone and its side chains by introducing fluorine and chlorine atoms (halogens), significantly increased the activity of external steroids used in modern medicine and veterinary medicine [5].

Thus, the local action of GCS can be effective in the treatment of inflammatory skin diseases, especially if the dermatitis is

localized, then it is necessary to carefully choose the dose and type of GCS that is suitable for the patient. The choice of corticosteroids should be based on the signs and type of disease of the animal, that is, the choice depends on the type of dermatosis, the area of the treated surface, the localization of the skin area, and the state of health of the animal [6, 7].

Materials and Methods

In this work, we used information retrieval databases, foreign sites, and scientific articles, as well as methods of analysis and generalization of information.

Results and Discussion

The mechanism of action of GCS

Corticosteroids by passive diffusion penetrate the cell membrane into the cell and bind in its cytoplasm with specific protein receptors. Then, the bound GCS with its specific receptor is transported into the cell nucleus, where, as a result, it binds to specific elements of the glucocorticoid response in DRA, while GCS can exhibit both inhibitory and stimulating effects.

Many synthetic drugs do not bind well to proteins, which is partly why they are highly effective even at low doses. There is a corticosteroid-binding globulin (specific glycoprotein), that binds glucocorticoids. However, its production is limited, therefore, if a large amount of GCS enters the body, it is albumin, that will act as a protein that binds these excess hormones. In this regard, for some patients, hypoalbuminemia may be critical, provided there is a significant intake of GCS in the framework of one or another glucocorticoid therapy [8-10].

Classification and rules for the use of local GCS

Glucocorticosteroids are factors in the natural reactivity of the immune system and cause the following pharmacological effects:

- anti-inflammatory effect: regardless of the cause of damage, corticosteroids interact nonspecifically with all components of the inflammatory response (suppressive effect on T-effectors of hypersensitivity, T-helpers). They reduce capillary dilation and exudation, inhibit leukocyte migration and phagocytic activity, reduce fibrin deposition and prevent scar tissue formation;
- impact on the immune response: in high doses, they reduce the production of lymphocytes and immunoglobulins, as well as the function of monocytes and macrophages. This leads to impaired immunocompetence. Violation of cell migration leads to an increase in the content of eosinopenia neutrophils;
- effects on carbohydrate and protein metabolism: stimulate gluconeogenesis, reduce glucose utilization in peripheral tissues, which leads to hypoglycemia. There is also a parallel increase in protein catabolism with the mobilization of amino acids from peripheral tissues;
- impact on water and electrolyte balance: increased sodium reabsorption and excretion of potassium and hydrogen ions. Hypernatremia can rarely induce hypertension in animals with heart failure;
- effects on fat metabolism: redistribution of fat;
- increased production of hydrochloric acid and pepsin in the stomach [11, 12].

Based on the wide range of pharmacological and physiological reactions of corticosteroids, their side effects are easily predictable:

- metabolic effects (obesity in the abdomen, muscle weakness, proximal myopathy - mainly in dogs; hyperglycemia, glucosuria - especially in cats; in dogs, diabetes mellitus rarely develops, requiring insulin therapy);
- capillary fragility;
- increased susceptibility to infections.

Drugs in this group are very active, but side effects (dysfunction of the adrenal glands, progression of diabetes mellitus, disorders of mineral metabolism, poor wound healing, etc.) oblige them to be moderately prescribed, if necessary, the dose should be reduced as soon as possible. The mode of application of GCS every other day causes less suppression of the function of the adrenal glands. Short-term therapy can be stopped quickly without much difficulty, long-term therapy (more than 4 weeks) requires gradual withdrawal over several weeks. Local use of GCS significantly minimizes side effects on the animal's body. Local application is a convenient option, since the drug acts directly on the area of inflammation, avoiding general exposure. Hydrocortisone-containing drugs - betamethasone, triamcinolone, and prednisolone - are effective in cases of various inflammatory dermatoses, including atopic dermatitis in dogs and cats. Hydrocortisone is of moderate action, prednisolone is more potent, and fluorinated corticosteroids such as dexamethasone, triamcinolone, betamethasone are the most potent. In veterinary practice, the most popular in terms of the effectiveness of treatment are prednisolone, dexamethasone, and hydrocortisone [13, 14].

The recommended doses of drugs of the GCS group are given in the table **(Table 1)**.

Table 1. Daily doses of corticosteroids for dogs and cats

Glucocorticosteroid	Dogs	Cats	Multiplicity of reception
Prednisolone	0,25-2,0 (5-10) mg / kg	0,5-2,0 (5-10) mg / kg	12-24 hours
Dexamethasone	0,1-1,25 mg / kg	0,125-1 mg / kg	12-24 hours
Hydrocortisone	0,5/mg / kg (5 mg / kg)	0,5 mg / kg (10 mg / kg)	12-24 hours

Hydrocortisone aceponate, which accumulates in the skin of dogs, is topical at low doses. Application of diesters to the skin results in a high therapeutic index - high activity with reduced systemic secondary effects. In addition, the product has a minimal effect on epidermal cells and collagen synthesis, which is a condition that prevents pronounced atrophogenicity. But, despite this, the drug should be applied with caution to those areas where the skin is physiologically thinned (scrotum, groin, armpits, sides) [15].

If we are talking about possible side effects arising from the use of glucocorticoids, then their list includes atrophy, peeling, comedones, alopecia, and pyoderma, as well as calcification of the skin, which can occur on their own, without concomitant systemic effects.

The most powerful corticosteroids are fluoride steroids. They penetrate the skin better and are therefore more effective. Even a single application to the skin during the day may be sufficient to achieve the expected effect. However, their use can be associated with a large number of side effects. Local glucocorticoid therapy should follow the same principles that apply to systemic therapy. That is, strong drugs at the initial stage should be used twice a day to relieve inflammation, then once a day, and finally, subject to the availability of the proposed long-term therapy, they should be replaced with milder" glucocorticoids. In the future, supportive therapy with these local agents should be continued, if possible, every other day.

Animals with atopic dermatitis generally respond well to GCS treatment. At anti-inflammatory doses, these drugs suppress many of the genes responsible for the production of cytokines and adhesion molecules, while antibodies such as IgEare produced at the same level. Therefore, the local application of GCS is indicated for the local manifestation of atopic dermatitis.

Not all inflammatory skin diseases require the appointment of corticosteroids, as for generalized demodicosis and skin infection, the use of corticosteroids, in this case, is usually contraindicated. However, otitis externa, immune-mediated and allergic skin diseases are the most common reasons for prescribing GCS. Most cases of immune-mediated skin diseases require the use of stronger GCS than in the treatment of allergic or irritating dermatitis. It is also necessary to avoid long-term topical use of GCS (in the form of lotions, sprays, gels, creams, ointments) due to the possibility of developing cutaneous atrophy [16].

Currently, there are several classifications, according to which corticosteroids for external use are divided into different groups and classes. First of all, they are divided into: analogs of natural hormones (cortisone, hydrocortisone); synthesized analogs (prednisolone), and their derivatives (halogenated, fluorinated). Of the non-fluorinated TGCS for external use, there are hydrocortisone acetate, hydrocortisone butyrate, prednisolone, and prednisolone derivatives (mometasonefuroate, mazipredone, methylprednisoloneaceponate). Among the fluorinated corticosteroids: dexamethasone, betamethasone, flucinolone, flumethasone, etc.

The classification of the activity of topical steroids can be based on the data of the vasoconstrictor test, which assesses the degree of vasoconstriction ("blanching effect") in healthy animals.

The most popular is the European classification, based on the clinical effectiveness of TCGS, according to which they are divided into 4 classes: weak, moderate, strong, and very strong, presented in the table **(Table 2)**.

Table 2. European classification of the activity of topical glucocorticosteroids

Class (degree of activity)	International non-proprietary name
Very strong (class IV)	Clobetasol propionate 0.05% Chalcinonide 0.1% Betamethasone valeriate 0.1% Betamethasone dipropionate 0.05% Budesonide 0.0375% Mometasonefuroate 0.1% Hydrocortisone 17-butyrate 0.1%
Strong (class III)	Dexamethasone 0.025% Triamcinolone acetonide 0.1% Methylprednisolone aceponate 0.1% Flumethasonepivalate 0.02% Fluocinoloneacetonide 0.025% Fluticasone propionate 0.05%
Medium strength (class II)	Prednisolone 0.25% Prednikarbat 0.25% Fluocortolone 0.025% Alclomethasonedipropionate 0.05%
Weak (class I)	Hydrocortisoneacetate 0.1%, 0.5%

The American Academy of Dermatology prefers classification in the reverse order from super strong grade 1 to least active grade 7 **(Table 3)**.

Table 3. American classification of the activity of topical glucocorticosteroids

Class (degree of activity)	International non-proprietary name
I - very strong	Clobetasol 0.05% cream, ointment Betamethasone (dipropionate) 0.1% cream, ointment; 0.05% cream, ointment
II - strong	Mometasone (furoate) 0.1% ointment, cream, solution Triamcinolone acetonide 0.1% ointment
III - moderately strong	Betamethasone (valerate) 0.1% cream, ointment Fluticasone (propionate) 0.005% ointment, 0.05% cream
IV - medium strength	Fluocinoloneacetonide 0.025% ointment, cream, gel, liniment Mometasone (furoate) 0.1% ointment, cream, solution Triamcinolone acetonide 0.025% ointment Methylprednisolone aceponate 0.1% fatty ointment, ointment, cream, emulsion
V - medium strength	Betamethasone (valerate) 0.1% cream Hydrocortisone (butyrate) 0.1% ointment, cream, emulsion, solution Fluocinoloneacetonide 0.025% cream, gel, liniment
VI - medium strength	Alclomethasone (dipropionate) 0.05% ointment, cream
VII - weak	Hydrocortisone (acetate) 0.5%, 1% ointment Prednisolone 0.5% ointment

When using topical GCS, there is a local increase in the concentration of corticosteroids in the area of the inflammatory process, due to which GCS does not have a suppressive effect both on the immune system and on other body systems, which avoids severe side effects [17].

Dosage forms with TGCS

The choice of a specific drug depends primarily on the disease and the location of the lesion. Depending on the type of pathology and the area to be treated, the active ingredient, the dosage form, and the concentration are selected, respectively.

For example, high-strength topical corticosteroids are used to treat exacerbations of alopecia areata, resistant (persistent) atopic dermatitis, and severe contact dermatitis. Topical corticosteroids of medium strength are used for atopic eczema, atopic dermatitis, and several other diseases. Topical corticosteroids belonging to the "weak" category are indicated as long-term maintenance therapy.

Topical steroids can be prescribed by veterinarians for exacerbations of dermatological diseases before the onset of remission, and the treatment of chronic inflammation.

The effectiveness of external dermatological agents in general and TGCS, in particular, depends on many reasons, and above all on the speed of their penetration into the epidermis and dermis. Topical corticosteroids can penetrate the skin in two ways: directly through the epidermis or through open hair follicles, sebaceous, and sweat glands. The main route of penetration of TGCS is transepidermal. The penetration of TGCS through the skin depends on six main factors: the place of application of the drug, the age of the pet (patient), the properties of the active ingredients, the basis of the drug, the method of its application, the stage of the disease (a skin condition) [18, 19].

The pharmacological response to TGCS is determined by four main points:

1. First of all, the different permeability of the skin, which depends on the localization of its lesion, as well as the presence of hair. The structure of the skin in different parts of the animal's body is significantly different, and accordingly, its permeability is also different. High sensitivity is characteristic of folds and other large folds, as well as the groin area, where the drug penetrates tens of times faster.
2. Concentration gradient, which shows the amount of the drug transferred into the skin per unit of time and directly depends on the concentration of the drug in the base, the coefficient of its release from the base, and the diffusion coefficient for a given thickness of the stratum corneum.
3. A dosage regimen that can be once a day and at the same time quite effective, given that the skin has the property of active absorption and reservation of the drug with its long "local half-life".
4. The basis of the drug and occlusion, which contribute to the maximum penetration of the drug through the epidermal barrier and by their physical properties, namely: drying, moisturizing, obesity or applied in a certain way (in the form of compresses), increase the absorption of the drug [20, 21].

Therapeutic success is facilitated not only by a properly selected drug but also by its dosage form, depending on the stage of inflammation, which determines the depth of penetration of the drug into the skin. The degree of this penetration is maximal when using TGCS in the form of an ointment, much less in the form of a cream, and very insignificant in the form of a solution (lotion). Dry skin is inaccessible for the penetration of an external corticosteroid, but maceration and moisturizing of the stratum corneum of the epidermis with an ointment base several times increase the permeability of the skin. Therefore, in case of chronic dermatoses, accompanied by dryness, peeling, lichenification, it is more advisable to use ointments and ointments on a fat basis. In acute processes with edema, vesiculation, preference is given to lotions, aerosols, oleogels, creams, and lipo-creams. Thus, it becomes clear that the use of topical corticosteroids is advisable due to their local action on activated cells in the skin [22, 23].

Scientists have conducted a significant amount of research confirming that long-term local use of GCS can lead to systemic changes: for example, adversely affect the response of the adrenal cortex to exogenous corticotropin and lead to an increase in the level of liver enzymes. And therefore, despite a significant number of preparations containing GCS in their composition, the search for safe means for topical application to the skin is relevant [24].

Conclusion

It should be noted that the group of topical GCS drugs currently continues to be the main one in the treatment of a large number of dermatoses, inflammatory genesis, due to its high efficiency, the possibility of high-quality management of dermatological health, and the rapid restoration of the patient's (pet's) quality of life.

Topical corticosteroids have pronounced anti-inflammatory, anti-allergic, anti-exudative, and antipruritic effects. They inhibit the accumulation of leukocytes, the release of lysosomal enzymes and anti-inflammatory mediators in the focus of inflammation, inhibit phagocytosis, reduce vascular tissue permeability, and prevent the formation of inflammatory edema.

The basis of the drug, as a rule, is selected depending on the topic of the inflammatory process. It is advisable to apply lotions, aerosols, gels, and creams that do not contain a fat base on the hairy parts of the body and folds. With highly infiltrated processes, an increase in the concentration and depth of penetration of the drug into the skin can be achieved by applying GCS in the form of a compress (under an occlusive dressing).

As several studies have shown, creams are usually less effective than ointments, even if they contain the same chemical composition as GCS. Creams contain preservatives that can cause local skin reactions. Lotions, gels, and foams containing GCS are not often used in veterinary dermatology, since lotions often

contain alcohol, and gels are less greasy and dry quickly. Ointments, in turn, due to the fatty base, give a quick release of GCS, but because of the hairy body of the animal, they are also not promising for use.

At the same time, the development of a line of drugs with various GCS for local use is a very urgent task of modern pharmacy.

Acknowledgments: I would like to thank all authors for their extraordinary support in this thesis process.

Conflict of interest: None

Financial support: None

Ethics statement: None

References

1. Soboleva MS, Loskutova EE, Kosova IV, Amelina IV. Problems and the Prospects of Pharmaceutical Consultation in the Drugstores. Arch Pharm Pract. 2020;11(2):154-9.
2. Sergeevna SM, Efimovna LE, Irina K. Pharmaceutical consultation as a basis for drug care continuity. Pharmacophore. 2020;11(4):76-82.
3. Aharon MA, Prittie JE, Buriko K. A review of associated controversies surrounding glucocorticoid use in veterinary emergency and critical care. J Vet Emerg Crit Care. 2017;27(3):267-77. doi:10.1111/vec.12603.
4. Leclere M. Corticosteroids and Immune Suppressive Therapies in Horses. Vet Clin North Am Equine Pract. 2017;33(1):17-27. doi:10.1016/j.cveq.2016.11.008.
5. Okanishi H, Nagata T, Nakane S, Watari T. Comparison of initial treatment with and without corticosteroids for suspected acute pancreatitis in dogs. J Small Anim Pract. 2019;60(5):298-304. doi:10.1111/jsap.12994.
6. Saridomichelakis MN, Olivry T. An update on the treatment of canine atopic dermatitis. Vet J. 2016;207:29-37. doi:10.1016/j.tvjl.2015.09.016.
7. Nuttall T, Mueller R, Bensignor E, Verde M, Noli C, Schmidt V, et al. Efficacy of a 0.0584% hydrocortisone aceponate spray in the management of canine atopic dermatitis: a randomised, double blind, placebo-controlled trial. Vet Dermatol. 2009;20(3):191-8. doi:10.1111/j.1365-3164.2009.00756.x.
8. Olivry T, DeBoer D, Favrot C, Jackson H, Mueller R, Nuttall T. Treatment of canine atopic dermatitis: 2015 update guidelines from the International Committee on Allergic Diseases of Animals (ICANA). BMC Vet Res. 2015;11(1):210. doi:10.1186/s12917-015-0514-6.
9. Sauve F. Use topical glucocorticoids in veterinary dermatology. Can Vet J. 2019;60(7):785-8.
10. O'Neill D, Hendricks A, Summers J, Brodbelt D. Primary care veterinary usage of systemic glucocorticoids in cats and dogs in three UK practices. J Small Anim Pract. 2021;53(4):217-22. doi:10.1111/j.1748-5827.2011.01190.x.
11. Nuttall T, Marsella R, Rosenbaum M, Gonzales A, Fabok V. Update on pathogenesis, diagnosis, and treatment of atopic dermatitis in dogs. J Am Vet Med Assoc. 2019;254(11):1291-300. doi:10.2460/javma.254.11.1291.
12. Igawa K. Future trends in the treatment of atopic dermatitis. Immunol Med. 2019;42(1):10-5. doi:10.1080/25785826.2019.1628467.
13. Santoro D. Therapies in Canine Atopic Dermatitis: An Update. Vet Clin North Am Small Anim Pract. 2019;49(1):9-26.
14. Becker D. Basic and clinical pharmacology of glucocorticosteroids. Anesth Prog. 2013;60(1):25-31. doi:10.2344/0003-3006-60.1.25.
15. Adcock I, Mumby S. Glucocoticoids. Handbook of experimental pharmacology. 2017;237:171-96. doi:10.1007/164_2016_98.
16. Klasa B, Cichocka-Jarosz E. Atopic Dermatitis – Current State of Research on Biological Treatment. J Mother Child. 2020;24(1):53-66. doi:10.34763/jmotherandchild.2020241.2003.0000010.
17. Hensel P, Santoro D, Favrot C, Hill P, Griffin C. Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification. BMC Vet Res. 2015;11:196. doi:10.1186/s12917-015-0515-5.
18. Marsella R, Ahrens K, Wilkes R, Trujillo A, Dorr M. Comparison of various treatment options for canine atopic dermatitis: a blinded, randomized, controlled study in a colony of research atopic beagle dogs. Vet Dermatol. 2020;31(4):284-e69. doi:10.1111/vde.12849.
19. Yan R, Jiang S, Wu Y, Gao X, Chen H. Topical calcipotriol/betamethasone dipropionate for psoriasis vulgaris: A systematic review. Indian J Dermatol Venereol Leprol. 2016;82(2):135-44. doi:10.4103/0378-6323.175919.
20. Williams D. Clinical Pharmacology of Corticosteroids. Respir Care. 2018;63(6):655-70. doi:10.4187/respcare.06314.
21. Kuehl B, Shear N. The Evolution of Topical Formulations in Psoriasis. Skin Therapy Lett. 2018;23(4):5-9.
22. Holland E, Fingeret M, Mah F. Use of Topical Steroids in Conjuctivitis: A Review of the Evidence. Cornea. 2019;38(8):1062-7. doi:10.1097/ICO.0000000000001982.
23. Raposo S, Simoes S, Almeida A, Ribeiro H. Advanced systems for glucocorticoids' delivery. Expert Opin Drug Deliv. 2013;10(6):857-77. doi:10.1517/17425247.2013.778824.
24. Pul-Luzan V, Rukhmakova O. Experimental substantiation of the composition of gel base with hydrocortisone for use in veterinary medicine. ScienceRise: Pharm Sci. 2021;31(3):4-10. doi:10.15587/2519-4852.2021.233664