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TUTORIAL

Clinical pharmacology review for primary health care providers: II. Steroids

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Primary health care providers play a critical role in maintaining public health, and the appropriate prescription of pharmaceutical products is a major component of their practice. This series of articles entitled 'Clinical Pharmacology Review for Primary Health Care Providers' is intended to help primary health care providers select more appropriate prescriptions for frequently used drugs based on up-to-date information. We expect that this effort will contribute to improvements in public health and diminish unnecessary drug use.

Introduction

Steroids are comprised of a group of cyclic organic compounds synthesized from cholesterol that share the basic 17-carbon, four-ring cholesterol structure. Hormones released from the adrenal cortex (corticosteroids), sex hormones, and bile acids are natural steroids that function in the body. However, in clinical medicine, the use of the term "steroid" is mostly limited to corticosteroid-like (particularly glucocorticoid-like) synthetic compounds. This article focuses on the clinical pharmacology and use of synthetic glucocorticoids and provides essential knowledge for the use of steroids in primary care environments.

Steroids simultaneously affect various physiological pathways and can induce multiple reactions including alterations in the immune response, metabolism, nervous system, and fluid homeostasis.[1,2] These broad effects of steroids are the main reason to fear their use, since undesirable responses or side effects are common. Despite these issues, steroids are widely prescribed by primary care physicians because they have clear benefits which outweigh the risks when used appropriately.[3,4] Thus, to optimize the outcomes of steroid therapy, physicians should be aware of the characteristics of each steroid compound to select the most suitable compound, dose and treatment duration for the specific disease condition. In addition, primary health care providers should perform proper monitoring and management of their patients undergoing steroid therapy based on up-to-date information.

GENERAL PRINCIPLES OF GLUCOCORTICOID USE

In general, in a primary care environment, steroid prescriptions are limited to low-dose, short-term and/or topical (not systemic) therapy. Even though the risk of steroid therapy is lower in these cases, some side effects can still occur (Table 1).[5,6] To avoid toxicity, the following general principles should be followed:

1. Consider applicable treatment options other than steroids,
2. Start steroid treatment only if symptoms are clearly definitive and other treatment options are inappropriate,
3. Use short- and intermediate-acting agents (avoid long-acting agents),
4. Prescribe the minimum necessary dose for the minimum necessary duration,
5. Topical agent should be selected whenever possible,
6. Beware of drug interactions.[5]

Accordingly, the actual selection of the specific steroid agent should be based on the pharmacokinetic (PK)-pharmacodynamic (PD) properties of each glucocorticoid.

CLINICAL PK-PD OF GLUCOCORTICOIDS

Many steroid compounds and dosage forms have been developed for the treatment of inflammatory, hematologic, and other disorders. In some cases, the agent given is a prodrug; for example, prednisone is rapidly converted to the active product prednisolone in the body. Thus, steroid agents with an appropriate PK-PD profile can be used for specific purposes. The clinically applicable PK-PD characteristics of steroid agents are summarized in Table 2.[1,7-9] Synthetic corticosteroids are rapidly and completely absorbed when given by mouth and in most cases show rapid onset of drug activity. Thus, the most important parameter used for classifying steroid agents is duration of action. Duration of action is determined by various factors including the free fraction in plasma, affinity to 11β-hydroxysteroid dehydrogenase 2 (the metabolic enzyme), lipophilicity, and target binding. In general, the duration of action is proportional to the degree of anti-inflammatory activity[10]; however, physicians should be aware that duration is not proportional to the intrinsic potency of each analogue. The actions of the steroid analogs are similar to those of the intrinsic glucocorticoid–cortisol. Each analog has a different glucocorticoid-to-mineralocorticoid potency ratio, and as a result, the fluid retention produced by the use of each agent may vary.

Table 1. Side effects of short-term glucocorticoid therapy

Gastrointestinal intolerance
Increased predisposition to infections
Delayed wound healing
Increased appetite
Hyperglycemia
Fluid and sodium retention
Mood changes
Weakness
Insomnia
Amenorrhea
Reduced sexual functioning (Impotence)
Difficulty or pain while urinating
Breast reduction
Acne
Rapid weight gain
Increased blood pressure and cholesterol levels
Headaches
Swelling of feet and ankles

NON-SYSTEMIC USE OF GLUCOCORTICOIDS

Glucocorticoids are more frequently used non-systemically as inhalants for airway diseases and as topical formulations for skin diseases. These are the most common reasons for steroid prescription at the primary care level, and treatment is often initiated at this level without specialist consultation.

Table 2. Pharmacokinetic-pharmacodynamic characteristics of corticosteroids for general use

Agent	Pharmacokinetics (oral)		Relative activities			Dosage forms	
	t_{max} (h)	$t_{1/2}$ (h)	Anti-Inflammatory	Topical	Salt-Retaining	Equivalent Oral Dose in mg (Relative potency)	Forms Available
Short- to medium-acting (<12 h)							
Hydrocortisone (cortisol)	1.2 ± 0.4	1.8 ± 0.5	1	1	1	20 (1.25)	Oral, injectable, topical
Cortisone			0.8	0	0.8	25 (1)	Oral
Prednisolone	1.3 ± 0.7	3.2 ± 1.0	4	0	0.3	5 (5)	Oral
Methylprednisolone	2.1 ± 0.7	2.5 ± 1.2	5	4	0.3	5 (5)	Oral, injectable
Meprednisone			5	5	0.25	4 (6.25)	Oral, injectable
Intermediate-acting (12–36 h)							
Triamcinolone	1	2	5	5	0	4 (6.25)	Oral, injectable, topical
Paramethasone			10		0	2 (12.5)	Oral, injectable
Fluprednisolone			15	7	0	1.5 (16.7)	Oral
Long-acting (>36 h)							
Betamethasone	2	8.1	25-40	10	0	0.6 (41.7)	Oral, injectable, topical
Dexamethasone	1.5	4.0 ± 0.9	30	10	0	0.75 (33.3)	Oral, injectable, topical

Inhalants

For the treatment of asthma, steroids are expected to have a broad anti-inflammatory, bronchial reactivity-reducing effect. If taken regularly, steroids may reduce the frequency of asthma exacerbations. Steroids have additional effects on the resolution of airway obstruction, but their main function is to inhibit the infiltration of asthmatic airways by immune cells.[1,11,12] Thus, inhalants can be a low side effect option for the effective improvement of all asthma symptoms, and oral formulations can be reserved for urgent or more severe asthmatic attacks.

The glucocorticoid analogs used as inhalants include beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, and triamcinolone. Ciclesonide is also administered in the form of a parent drug (without pharmacological activity), which further reduces local side effects; the drug is tightly bound to serum proteins, which minimizes systemic effects. Dose and administration frequency may vary, not by the active ingredients, but by the final drug product (formulation); thus, the prescribing physician should be well-informed of the instructions for each glucocorticoid inhalant. When used with oral glucocorticoid formulations for severe asthma symptoms, higher doses may be more effective and may increase the chance of oral treatment cessation.[1] In these cases, the incidence of local and systemic side effects may increase, and patients should be monitored carefully. One of the most problematic consequences of inhalant corticosteroid treatment is oropharyngeal candidiasis.[13] This can be prevented by having patients gargle and spit water after each administration.

Recently, the use an inhaled corticosteroid combined with a long-acting β agonist has become common. Combination inhalers are convenient, ensure that the β agonist will not be taken alone (known to not protect against attacks), produce prompt and sustained improvements in clinical symptoms and pulmonary function, and reduce the frequency of exacerbations requiring oral corticosteroid treatment.[10,14,15] For patients using such formulations, a rapid-acting inhaled β2 agonist, such as albuterol, may be needed to relieve acute symptoms.

Topical skin formulations

Glucocorticoids have mainly anti-inflammatory and antimitotic effects on the skin, and their use is indicated for inflammatory diseases and diseases involving increased cell proliferation (e.g. psoriasis).[16] Since corticosteroids are incredibly effective at treating inflammatory skin diseases, numerous analogs of various potencies, concentrations, and vehicles are now available (Table 3). The potency of each analogue is identical to that shown in Table 2; however, the actual efficacy of each formulation may be adjusted by modifying the concentration of the active ingredient.

Agents should be selected according to the area of application. Glucocorticoids are minimally absorbed when applied to normal skin; however, the amount absorbed by the skin may vary greatly based on the thickness of the epithelium.[16] For

Table 3. Topical corticosteroids in various formulations summarized by Robertson DB & Maibach HI

Concentration	Drug
Lowest efficacy	
0.25–2.5%	Hydrocortisone
0.25%	Methylprednisolone acetate (Medrol)
0.1%	Dexamethasone[1] (Decaderm)
1.0%	Methylprednisolone acetate (Medrol)
0.5%	Prednisolone (MetiDerm)
0.2%	Betamethasone[1] (Celestone)
Low efficacy	
0.01%	Fluocinolone acetonide[1] (Fluonid, Synalar)
0.01%	Betamethasone valerate[1] (Valisone)
0.025%	Fluorometholone[1] (Oxylone)
0.05%	Alclometasone dipropionate (Aclovate)
0.025%	Triamcinolone acetonide[1] (Aristocort, Kenalog, Triacet)
0.1%	Clocortolone pivalate[1] (Cloderm)
0.03%	Flumethasone pivalate[1] (Locorten)
Intermediate efficacy	
0.2%	Hydrocortisone valerate (Westcort)
0.1%	Mometasone furoate (Elocon)
0.1%	Hydrocortisone butyrate (Locoid)
0.1%	Hydrocortisone probutate (Pandel)
0.025%	Betamethasone benzoate[1] (Uticort)
0.025%	Flurandrenolide[1] (Cordran)
0.1%	Betamethasone valerate[1] (Valisone)
0.1%	Prednicarbate (Dermatop)
0.05%	Fluticasone propionate (Cutivate)
0.05%	Desonide (Desowen)
0.025%	Halcinonide[1] (Halog)
0.05%	Desoximetasone[1] (Topicort L.P.)
0.05%	Flurandrenolide[1] (Cordran)
0.1%	Triamcinolone acetonide[1]
0.025%	Fluocinolone acetonide[1]
High efficacy	
0.05%	Fluocinonide[1] (Lidex)
0.05%	Betamethasone dipropionate[1] (Diprosone, Maxivate)
0.1%	Amcinonide[1] (Cyclocort)
0.25%	Desoximetasone[1] (Topicort)
0.5%	Triamcinolone acetonide[1]
0.2%	Fluocinolone acetonide[1] (Synalar-HP)
0.05%	Diflorasone diacetate[1] (Florone, Maxiflor)
0.1%	Halcinonide[1] (Halog)

Table 3. Continued

Concentration	Drug
Highest efficacy	
0.05%	Betamethasone dipropionate in optimized vehicle (Diprolene)[1]
0.05%	Diflorasone diacetate[1] in optimized vehicle (Psorcon)
0.05%	Halobetasol propionate[1] (Ultravate)
0.05%	Clobetasol propionate[1] (Temovate)

[1]Fluorinated steroids

example, compared with the forearm, hydrocortisone is absorbed 0.83-, 6-, and 42-fold better through the palm, forehead, and scrotal skin, respectively. In addition, the application of additional skin protection such as impermeable film may result in a 10-fold increase in drug absorption. Severe skin diseases may require agents with higher efficacy; however, drug absorption is increased in these cases due to an impaired skin barrier. Thus, agent selection for these patients is complicated, and patients with such lesions should be referred to expert dermatologists rather than primary care physicians.

Ointment formulations generally have better activity than do creams or lotions.[16] The absorption of glucocorticoids increases with the concentration of the agent; however, the relationship is not linear, and an increase in absorption does not always result from an increase in concentration. To overcome the limited and variable percutaneous absorption of corticosteroids, insoluble corticosteroids, such as triamcinolone, acetonide, and betamethasone acetate-phosphate, may be injected intralesionally. After injection, the glucocorticoids are released slowly from the injection site over several weeks.

Skin atrophy can occur as a side effect and must be monitored. This complication may present as depressed, shiny, and often wrinkled skin and can result in the development of secondary skin lesions which are hard to treat.[16,17] Topical corticosteroids are contraindicated in individuals who demonstrate hypersensitivity. Some sensitized subjects develop a generalized flare when given adrenocorticotropic hormone or oral prednisone.

SYSTEMIC USE OF GLUCOCORTICOIDS

Glucocorticoids are used systemically for diseases indicating steroid use. Originally, the primary indication for glucocorticoid use was to treat insufficient hormone production from the adrenal cortex. However, glucocorticoids, due to reasons discussed previously, have a large range of applications, including acute attenuation of certain diseases (short-term high dose), treatment of chronic diseases, treatment for immunosuppression that cannot be controlled without steroids (long-term low dose), and in combination with cancer chemotherapy (Table 4). However, these conditions cannot be initiated or maintained in the primary care environment; thus, the primary care provider should focus on monitoring side effects rather than actually

Table 4. Indications for the use of glucocorticoids in nonadrenal disorders

Disorder	Examples
Allergic reactions	Asthma, bee stings, contact dermatitis, allergic rhinitis, serum sickness, urticaria
Collagen-vascular disorders	Lupus erythematosus, mixed connective tissue syndromes, polymyositis, rheumatoid arthritis, temporal arteritis
Eye diseases	Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis
Gastrointestinal diseases	Inflammatory bowel disease, nontropical sprue, subacute hepatic necrosis
Hematologic disorders	Acquired hemolytic anemia, acute allergic purpura, leukemia, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, multiple myeloma
Systemic inflammation	Acute respiratory distress syndrome
Infections	Acute respiratory distress syndrome, sepsis
Joints inflammation	Arthritis, bursitis, tenosynovitis
Neurologic disorders	Cerebral edema, multiple sclerosis
Organ transplants	Prevention and treatment of rejection (immunosuppression)
Pulmonary diseases	Aspiration pneumonia, bronchial asthma, fetal lung maturation, sarcoidosis
Renal disorders	Nephrotic syndrome
Skin diseases	Atopic dermatitis, dermatoses, mycosis fungoides, pemphigus, seborrheic dermatitis, xerosis
Thyroid diseases	Malignant exophthalmos, subacute thyroiditis
Miscellaneous	Hypercalcemia, mountain sickness

Table 5. Various systemic side effects of long-term glucocorticoid use

Major	Minor
Increased blood sugar for diabetics	Nervousness
Difficulty controlling emotion	Acne
Weight gain	Skin rash
Immunosuppression	Appetite gain
Facial swelling	Hyperactivity
Depression, mania, psychosis	Increased thirst
Unusual fatigue or weakness	Frequent urination
Mental confusion / indecisiveness	Diarrhea
Blurred vision	Reduced intestinal flora
Abdominal pain	Leg pain/cramps
Peptic ulcer	Sensitive teeth
Painful hips or shoulders	
Steroid-induced osteoporosis	
Insomnia	
Severe joint pain	
Cataracts or glaucoma	
Anxiety	
Black stool	
Stomach pain or bloating	
Severe swelling	
Mouth sores or dry mouth	
Avascular necrosis	
Hepatic steatosis	

prescribing glucocorticoids. In addition, drug interactions should be considered in the primary care environment, since newly prescribed drugs may interact with steroids used to treat chronic diseases and can result in drug-response changes.

Systemic side effects of long-term glucocorticoid treatment

Primary care providers should be able to notice the systemic adverse effects of long-term glucocorticoid use (Table 5) and be able to notify physicians with adequate expertise in these effects so that the therapy might be adjusted.[1,5] Careful review of a patient's medical history, a thorough physical examination, and vital sign and weight checkups may help identify side effects. These procedures may enable the early detection of side effects and facilitate personalized glucocorticoid treatment that optimizes outcome and reduces side effects and costs.

More attention should be paid to children and elderly patients, who are more prone to developing side effects. For children, growth retardation may occur as a consequence of systemic steroid therapy.[18-20] Even though it is unlikely, growth retardation is possible in children receiving local steroid therapy for diseases such as asthma or atopic dermatitis. Elderly patients may suffer imbalances in glucose and lipid homeostasis and bone metabolism.[21,22] However, the sensitivity of elderly patients to side effects is reduced such that side effects are rarely discovered until symptoms become severe. For pregnant women, prednisone can be used safely without fetal risk, because it is not transformed into active prednisolone by the liver of the fetus, and maternal prednisolone is not transported to the fetus via the placenta. However, to secure safety, use of steroids should be carefully considered and the patient's wishes taken into account. In addition, obstetrics experts should be referred to whenever possible.

Drug interactions related to glucocorticoid treatment

Steroids may reduce the therapeutic effectiveness of drugs such as glucose-lowering agents, antihypertensives, diuretics, and heparin.[23] The effectiveness of steroids may be diminished by drugs including rifampicin, carbamazepine, phenobarbitone and phenytoin, and steroids may potentiate the side effects of other drugs, including the hypokalemic effect of diuretics and ulcerogenic effect of non-steroidal anti-inflammatory drugs.[23] Thus, when prescribing the drugs listed above, all physicians involved should discuss the treatment plan carefully.

SUMMARY

Steroids are one of the most effective treatment options in many disease conditions when used appropriately. Primary health care providers can utilize steroid agents based on the general prescription principles and PK-PD of steroid. Careful monitoring for adverse effects in all patients receiving steroid may enhance the effectiveness of treatment while minimizing undesired consequences.

Conflict of interest

None of the authors have any conflicts of interest to disclose.

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