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Review Article

Corticosteroids-The Life-Saving Drugs in Chronic Diseases

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Abstract

Corticosteroids are therapeutic drugs used in the management of various diseases. They are vastly used in the field of medicine for treating chronic diseases. Steroids act as drugs of choice when the rest of the drugs failed in the due course of the management of illness. Even during the Covid-19 pandemic steroids stood as hope for treatment. Corticosteroids always act as a cure for chronic diseases despite their known Adverse effects. They always stand as hope for the clinician in restoring the health and vigour of the patient. In this article, we shall discuss corticosteroids and their applications in the management of chronic diseases in medicine and dentistry.

Keywords: Corticosteroids; Glucocorticoids; Mineralocorticoids

Introduction

The term corticosteroids include natural glucose and mineral corticoids and their synthetic analogues. Natural corticosteroids are secreted by adrenal glands [1-10].

Adrenal Glands

A pair of Adrenal glands are present above the Kidney. They consist of the outer cortex and inner medulla.

Adrenal Cortex

- Zona Glomerulosa Secretes Aldosterone, a Mineralocorticoid which regulates water and electrolyte metabolism.
- Zona fasciculata secretes Cortisol, a Glucocorticoid which regulates carbohydrate, protein and
- mineral metabolism. It also has anti-inflammatory action.
- Zona Reticularis secretes sex harmones.

Adrenal medulla

Produces Adrenaline and Non-Adrenaline.

Functions

- Maintenance of B.P.
- Control of myocardial contractility and excitability.
- Regulation of body metabolism.

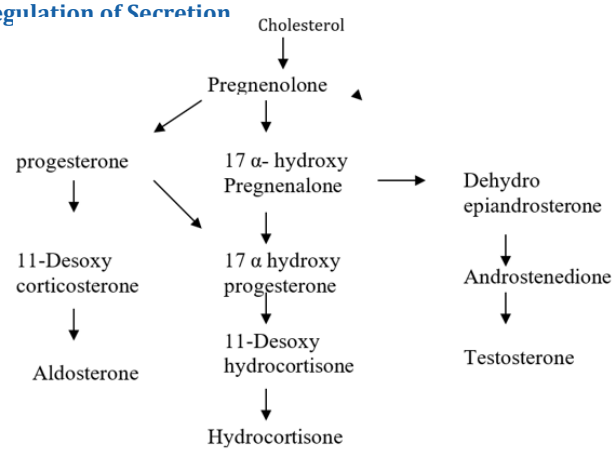
Chemistry of Steroids

The basic structure of steroids consists of 21 carbon compounds having a Cyclopentanoperhydro Phenanthrene ring with various functional groups attached to different carbon atoms.

Biosynthesis

Synthesis of steroids takes place in the Adrenal cortex by the cortical cells mediated by steroidogenic enzymes. The Source of the steroids is cholesterol which is obtained from LDL which is taken from circulation.

Regulation of Secretion



As a part of the normal circadian rhythm and during periods of stress CNS afferent nerves stimulate the hypothalamus to secrete Corticotropin-Releasing Hormone (CRH). Decreased plasma Cortisol concentration also by negative feedback mechanism stimulates the secretion of CRH. The released CRH via the portal circulation reaches the anterior pituitary and stimulates the basophilic cells to secrete Adrenocorticotropic Hormone (ACTH). The ACTH thus released into the blood Circulation reaches the Adrenal gland and stimulates the synthesis and release of Cortisol. This forms the Hypothalamic-Pituitary-Adrenal axis (HPA axis).

Aldosterone secretion is regulated by Renin released by the kidney when there is a decrease in sodium concentration and increase in potassium concentration which converts Angiotensinogen to Angiotensin I which is then converted into Angiotensin II by a converting enzyme from the lungs.

Adrenal cortical cells store only minute quantities of hormones,

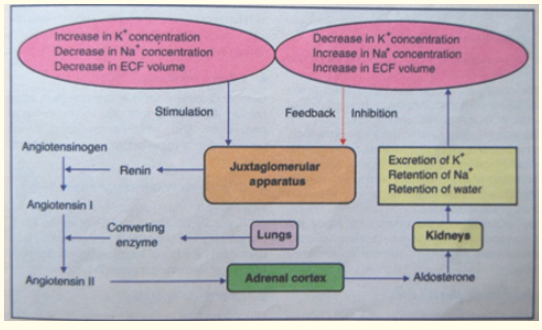


Figure 1

so the rate of release is governed by the rate of biosynthesis. The normal rate of secretion of corticoids in man are

- Hydrocortisone -10mg daily
- Aldosterone - 0.125mgdaily

Mechanism of action

Acts by a common mechanism at the cellular level.

2 receptor systems- glucocorticoid receptor

- Mineralocorticoid receptor.

Effects of steroids are mediated by interaction with specific receptors which form a steroid–receptor complex in the cytoplasm which enters the nucleus and influences the mRNA transcription of proteins. Lipocortin, a protein synthesized inhibits the activity of phospholipase which is required for the conversion of phospholipase to Arachidonic acid and so the release of inflammatory. Mediators Prostaglandins, Prostacyclins and Leukotrienes is inhibited.

Actions

Corticoids have some direct actions and some permissive actions. Permissive actions meanwhile do not themselves produce an effect, their presence facilitates other hormones to produce their action. Eg; Corticoids do not have any effect on B.P but their pressor action of Adrenaline is markedly blunted in their absence.

Glucocorticoids

The natural Glucocorticoids are –Hydrocortisone (Cortisol)

- Cortisone
- Corticosterone

Synthetic Glucocorticoids are

- Prednisone -Paramethasone
- Prednisolone -Dexamethasone
- Triamcinolone - Betamethasone

Synthetic steroids

Synthetic Steroids replaced natural steroids because

- Highly potent.
- Longer-acting.
- More selective for Glucocorticoid action.
- Possibility to prepare esters suitable for topical application and injection into tissues.

Physiological effects of glucocorticoids

Carbohydrate metabolism

- Promotes gluconeogenesis.
- Deposition of glycogen in the liver.
- Inhibits glucose utilization by peripheral tissues.
- Blood glucose levels increased.

Protein metabolism

- Catabolic in action.
- Amino acid mobilized is used in gluconeogenesis.
- Excess urea produced.
- Negative nitrogen balance.

Fat metabolism

- Play a 'permissive' role in the mobilization of fat from the peripheral fat depots by Adrenaline and Growth hormone.
- Redistribution of fat in the body, with loss from extremities and deposition over face, neck and shoulder causing Buffalo Hump, Moon-Face and Fish Mouth.

Electrolyte and water metabolism

- Causes Na retention and K excretion.
- Na retention causes water retention and oedema. This may produce a rise in Blood pressure.
- K excretion causes the wasting of muscles.

Calcium metabolism

- Inhibit intestinal absorption of calcium and enhance renal excretion of calcium.
- Stimulate the breakdown of the protein matrix of bone.
- Leads to osteoporosis.

Haematological actions

- Increase in the number of RBC, Neutrophils, and Platelets.
- Decrease in the number of Lymphocytes, Eosinophils, and Basophils.
- Brought about by the redistribution of the cells between the blood and other compartments.
- No lysis of Lymphocytes in the normal person.

Skeletal Muscles

- Optimum levels of corticoids are needed for normal muscle activity.
- Muscular weakness occurs in both Hypo and Hypercorticism.
- Hypocorticism: diminished work capacity and weakness are due to hypo dynamic circulation.
- Hypercorticism: excess mineralocorticoid action-hypokalemia-weakness.

Stomach

- Secretion of gastric acid and pepsin is increased.
- Aggravates peptic ulcer.

Lymphoid tissue

- Enhance the rate of destruction of lymphoid cells (T cells are more sensitive than B cells).
- The effect on normal lymphoid tissue is modest. However, a marked lytic response is shown by malignant lymphatic cells.

Anti-inflammatory effect

The anti-inflammatory effects are non-specific as the cause of the inflammatory reaction is not controlled. The possible mechanisms which possibly contribute to its action are

- Inhibit the recruitment of Neutrophils and macrophages into the affected area.
- Suppress the production of IL-1 by monocytes and IL-2 by lymphocytes.

Suppress the production of Lymphokines like TNF.

- Reduce the antibacterial activity of Monocytes.
- Inhibits the production of Plasminogen activator by Neutrophils.
- Inhibits release of arachidonic acid from phospholipids.
- Stabilize the lysosomal membranes thus preventing the spillage of hydrolytic enzymes.

Immunosuppressive action

- Decreased T cells.
- Decreased Cell-Mediated Immunity.
- Suppresses all types of hypersensitivity and allergic phenomena.
- It is used to prevent graft rejection, autoimmune diseases and organ transplants.

CNS

- Mood elevation.
- Euphoria.
- Nervousness.
- Restlessness
- Psychosis.

CVS

- Glucocorticoids have a permissive effect on the pressor action of Adrenaline and Angiotensin. They play a permissive role in the development of Hypertension, so should be cautiously used.
- They restrict capillary permeability and maintain the tone of arterioles and cardiac contractility.

Pharmacokinetics

- Administered orally, topically, parenterally and rectally.
- Well absorbed by any site of administration.

Transported in the plasma- bound to plasma protein.

- Metabolised in the liver.
- Rate of steroid metabolism- dependent on preparation.
- Methylprednisolone and Betamethasone are metabolised slowly as compared to hydrocortisone.

Preparations and Dosage

- Systemic Corticosteroids
  - Short acting
  - Intermediate acting
  - Long acting
- Topical Corticosteroids
  - Medium potency
  - High potency
  - Super potency
- Intralesional Corticosteroids

Systemic corticosteroids - indications

Severe or resistant oral ulceration in vesiculobullous conditions.

Multisystem diseases, such as Lichen planus with oral, genital and cutaneous Involvement

- Pemphigus
- Giant cell arteritis.
- Bell's palsy.

Principles for systemic steroid therapy

Single dose (even excessive) is not harmful. Short courses (even high doses) are not likely to be harmful in the absence of contraindications. Long term use is potentially hazardous; keep the dose to a minimum. No abrupt withdrawal after a corticoid has been given for more than 2-3 weeks; may precipitate adrenal insufficiency. Infection, severe trauma or any stress during corticoid therapy, increase the dose.

Hydrocortisone

- Orally given in Replacement Therapy.
- In Adults; 20 -30 mg daily in 2 div doses.
- In Children; 400-800 mcg/kg/day in 2 div doses.
- Intravenously given in Emergency treatment.
- In Adults; 100-500mg 3-4 times daily.
- In Children; 50 mg daily.

Prednisolone

Orally in Adults 2.5 -60 mg daily.

Parenterally

As Sodium phosphate ester; 4 -60 mg daily iv/im

Triamcinolone

Orally in Adults 4-48mg daily.

Parenterally: as acetonide; 20-80 mg.

as diacetate; 40 mg.

Betamethasone

Orally in Adults 0.5-5mg daily.

Parenterally as Sodium phosphate; 4-20 mg IV/IM.

Dexamethasone

- Orally in Adults 0.75 -9mg daily.
- Parenterally as Phosphates.

Systemic corticosteroid therapy

Systemic Corticosteroids are the most predictable medications used to control autoimmune diseases and certain immune-based inflammatory diseases.

The drug of choice is Prednisone, an anti-inflammatory glucocorticoid that affects mostly the cellular phase of inflammation, lymphocytes in particular.

There are 3 clinically effective Prednisone regimens.

The choice of the regimen should be based on the specific diagnosis, the intensity of the disease
and the organ systems involved.

Systemic corticosteroid regimen 1

The regimen begins with prednisone, 100 to 120 mg per day by mouth (1.5mg/kg/day) for 2 weeks.

A tapering schedule reduces prednisone by 20mg per day each week over several weeks until a dose of 20mg per day is reached.

This dose is continued for 1 month, followed by 10mg per day for 3months. The dose is then reduced to 10 mg every other day for another 3 months, followed by 5mg every other day for 6 months.

After 6months of a 5mg dose every day, the drug may be discontinued a high possibility of extended remission in a drug-free state.

The rationale of this approach is to gain a rapid suppression of the disease activity with a high loading dose and to taper this dose rapidly enough to avoid most of the serious side effects of high dose prednisone.

This regimen is the preferred regimen because it facilitates long term remission and has reduced the side effects. It is indicated for most oral lesions associated with Pemphigus Vulgaris, erosive lichen planus and severe non-ocular pemphigoid.

It is very effective but requires the close attention of the clinician and absolute compliance by the patient.

Systemic corticosteroid regimen II

This regimen begins with prednisone 100 to 120mg per day by mouth(1.5mg/kg/day) for a period of 2 weeks, at which time the drug is abruptly discontinued.

The rationale of this approach is to gain rapid suppression of disease activity and discontinue the drug before the side effects develop or significant adrenal suppression occurs.

This approach is effective and much more straightforward than regimen I.

Its drawback is that exacerbations are more frequent and the disease process is less controlled.

It is indicated in Pemphigus Vulgaris, erosive lichen planus and severe non-ocular pemphigoid. It is the preferred regimen in the Stevens-Johnson form of erythema multiforme.

Systemic corticosteroid regimen III (A)

This begins with prednisone 100 to 120mg per day by mouth for 2 weeks.

A tapering schedule reduces prednisone by 20 mg per day each week until the lowest possible prednisone level is reached without exacerbating the disease.

Many people remain on 20mg per day or even high doses for longer periods because fewer dosages are associated with disease exacerbations.

It is indicated in those cases with disease intensity and organ involvement that lower doses of prednisone cannot control.

It is usually applied to resistant Pemphigus cases and selected cases of systemic lupus erythematosus or sarcoidosis. These patients require lifelong adjustments and follow-up.

Systemic corticosteroid regimen III (B)

This regimen begins with 100 to 120 mg of prednisone per day by mouth for 2 weeks.

A tapering schedule reduces prednisone by 20 mg per day each week until a prednisone level is reached at which the disease is exacerbated.

This level and slightly higher levels of prednisone may still be associated with disease activity.

Cyclophosphamide 50 to 100mg….. twice daily by mouth;

Azathioprine 50 to 100mg …. twice daily by mouth

The rationale of this approach is to affect the disease with double drug therapy so that the dosage and therefore the side effects of each drug can be reduced.

This approach is reserved for refractory cases and for patients whose corticosteroid complications pose a greater risk such as those with diabetes, a history of Tuberculosis, peptic ulcer disease, osteoporosis and cataracts. It is also strongly recommended as a regimen for ocular pemphigoid.

Topical Corticosteroids

These are useful in the management of many ulcerative conditions there is no systemic involvement.

The application of more potent topical steroids also increases the likelihood of superimposed oral Candidiasis so better to advocate the concomitant use of the prophylactic, topical anti- fungal agent.

Recurrent aphthous stomatitis.

- Lichen Planus.
- Desquamative Gingivitis.
- Mucous membrane Pemphigoid.
- Psoriasis.
- Chronic Discoid Lupus Erythematosus.
- Allergic Contact Dermatitis.
- Hypertrophied scars and Keloids.

Guidelines for topical steroids

Steroids are used locally as a spray, gel or cream or as a mouthwash if they are erosive lesions.

Creams, gels, and sprays are better than ointments since the latter adhere poorly to the mucosa.

Steroids need to be in contact with mucosa for at least 3 min on each occasion.

Patients should not eat or drink for 30 min after using the steroid to prolong contact with the lesion.

They can be applied in a plastic splint worn overnight for Desquamative gingivitis.

In patients using potent steroids for more than a month, it is prudent to add an antifungal, since Candidiasis may arise.

Steroid mouthwashes

Made by dissolving a soluble Betamethasone sodium phosphate (0.5mg) tablet in 10ml of water and have to be held in the mouth for 3 min, before spitting out.

Used 3 times daily if required and should not be swallowed because of risks of systemic absorption.

Adverse Reactions secondary infection by Candida albicans.

Epidermal and Dermal atrophy (Thinning of the skin, striae, telangiectases, superficial fissures and purpura)

- Acne, Folliculitis.
- Hypertrichosis.
- Hypopimentation.

Intralesional steroids

These are useful in the management of intractable local lesions such as

- Erosive Lichen Planus
- Orofacial Granulomatosis.
- OSMF.
- Central Giant Cell Granuloma.

Intraarticular steroids

Indicated in Inflammatory joint disease, Rheumatoid Arthritis, and Acute Gouty Arthritis.

- Betamethasone sodium phosphate, 4 - 8mg
- Methyl Prednisolone acetate, 4 – 80 mg
- Triamcinolone acetonide, 2 – 3mg
- Triamcinolone hexacetonide, 2- 30mg

Inhalational Corticosteroids:

Used in the treatment of Chronic Persistent Asthma. Steroid inhalation is the first-line therapy

for chronic asthma.

Have anti-Inflammatory action and reduce bronchial hyperresponsiveness after exposure to the allergen.

Beclomethasone dipropionate, a halogenated corticosteroid ester is used in pressurized Metered. Dose Inhalation (MDI) which delivers 50 mcg of the drug-aerosol each time. Recommended 2-4 puffs 3-4 times a day.

Precautions during therapy

Before starting therapy

- Enquire and check for peptic ulcer, DM, Tuberculosis, or any other infections.

During therapy

- Prescribe the drug with food.
- Diet low in calories, sodium and high in potassium.
- Monitor growth in children.
- Check periodically for weight gain, edema, hyperglycemia, hypertension, infection. Monitor growth in children. Instruct patient not to stop the drug abruptly. Increase the dose in case of any stress.

While stopping therapy

- Taper therapy.

Pharmacotherapy Arthrititis

- Rheumatic arthritis
- Osteoarthritis
- Rheumatic fever
- Gout

In all the above arthritis, NSAIDs are the preferred drugs and are supplemented with corticosteroids

Collagen diseases

In Systemic Lupus Erythematosus, Polyarteritis nodosa, Dermatomyositis, Nephrotic syndrome and Glomerulonephritis may be lifesaving. Therapy is generally started with high doses which are tapered to maintenance doses when remission occurs.

Severe allergy

Corticoids may be used for short periods in Anaphylaxis, Urticaria and Serum sickness.

However, even i.v injection of steroid takes 1-2 hrs to act and is not a substitute for adrenaline (which acts immediately) in Anaphylactic shock and Angioneurotic oedema of the Larynx.

Autoimmune diseases

Autoimmune hemolytic anaemia, Thrombocytopenia, and active chronic hepatitis respond to corticoids.

Bronchial asthma

- Steroids are given I.V and withdrawn after the emergency is over in Status Asthmaticus.
- In severe Asthma it is given as a supplement to Bronchodilator.

Infective diseases

- A severe form of Tuberculosis
- Severe Lepra reaction
- Bacterial Meningitis
- Pneumocystis carnii pneumonia

In these conditions, Steroids are administered under effective chemotherapeutic cover to tide over the crisis or to prevent complications.

Skin diseases

- Pemphigus vulgaris
- Exfoliative dermatitis
- Steven Johnson syndrome

Topical steroids are highly effective and are widely employed.

Eye diseases

Ordinarily, steroids should not be given in infective conditions, but if inflammation is severe they may be applied in conjunction with effective antibiotics.

- Allergic conjunctivitis
- Iritis
- Retinitis
- Optic neuritis

Steroids are contraindicated in Herpes Simplex Keratitis and in their Occular injuries.

Intestinal diseases

In Ulcerative colitis, Crohn's disease and Coeliac diseases with remissions and exacerbations steroids are indicated during acute phases.

Cerebral edema

Due to tumours and Tuberculous meningitis respond to corticoids. Dexamethasone and Betamethasone are preferred because they do not have sodium retaining capacity.

Malignancies

- Acute Lymphatic Leukemia
- Hodgkin's Lymphoma
- Other Lymphomas

Steroids have marked lymphocytic action and are combined with chemotherapy.

Organ Transplantation and Skin Graft

High doses of corticoids are given along with another immunosuppressant to prevent rejection reaction followed by low maintenance doses.

Miscellaneous

- Bell's Palsy
- Acute infective Polyneuritis
- Infective Hepatitis

Dental applications

Recurrent aphthous ulcers (RAU)

Steroids used in RAU have 2 modes of action.

- Anti-Inflammatory action.
- Specific blocking effect of T-Lymphocyte –Epithelial cell interaction.

Oral lichen planus

- Topical: high potency steroids- 0.5% Flucinonide and 0.5% Clobetasol propionate.
- Extensive erosive OLP on gingiva (Desquamative gingivitis) treated with occlusive splints as carriers for topical steroids.
- Systemic steroids are indicated in cases recalcitrant to topical steroids
- Systemic Prednisolone 40 and 80 mg daily for < 10 days.

Oral submucous fibrosis

Corticosteroids prevent and suppress inflammatory reactions and prevent fibrosis by lowering fibroblast proliferation and deposition of collagen.

Dosage: Long-acting steroid Betamethasone (Betnesol) or Dexamethasone is injected Intralesional and submucosally at 2-4 days intervals for 1-4 months as per requirement.

Bell's palsy

Hurtado Gare., *et al.* (1997) treated 47 patients with Bell's palsy with an initial 60mg of Prednisolone and followed by steroids in a tapering regimen. 95% of the patients regained motor control.

Facial palsy secondary to herpes zoster infection

Ko Jy., *et al.* (2000) treated 30 patients suffering from Facial palsy secondary to Herpes Zoster infection of the Auriculotemporal region. A combination of parenteral Acyclovir and oral Prednisolone showed dramatic relief in most cases.

Desquamative gingivitis Pemphigus

- In severe cases of Pemphigus with widespread cutaneous and oral mucosal extension 180mg/day Prednisolone; lesions improve by the 5th day.
- If it does not, increase the dose to 250mg/day.
- To reduce the side effects, combination with Azathioprine 50-100mg/day.
- Once the disease has been controlled 40mg/day for 1 week, then 30mg/day the
- following week, 25mg/day the next week.
- 40mg/day on alternate days.

Discoid lupus erythematosus

- Prednisolone 40mg daily, early morning for 5 days controls the episode.
- Prednisolone 10-20mg for the following 2 weeks.
- Same dose on alternative days until the disappearance of lesion/ until symptoms
- are tolerated.
- Reduce periapical inflammatory response following endodontic treatment using topical and intradental routes of administration.
- Reduce post-operative pain and oedema after 3rd molar extraction.
- A combination of Hydrocortisone and Oxytetracycline can prevent alveolar osteitis.

Drug interactions and adverse effects

Thiazides may enhance hyperglycemia and hypokalemia caused by corticosteroids. Increased incidence of peptic ulcer or GI bleeding with concurrent NSAID administration. Response to anticoagulants is altered.

The dose of anti-diabetics and anti Hypertensives needs to be increased. Increased bioavailability with estrogens and oral contraceptives. Mutual inhibition of metabolism between Cyclosporine and Corticosteroids increases the plasma concentration of both drugs.

Reduced efficacy with concurrent use of Carbamazepine, Phenytoin, Primidone and Rifampicin.

Patients with adrenal gland disorders

Adrenal Adenoma

- Unilateral- no coverage of steroids required.
- If bilateral adrenalectomy is done: chronic steroid replacement.

Hypofunction of the adrenal gland

- Chronic steroid replacement.
- 10-20mg of Prednisolone- maintenance therapy.
- Increase the dose of steroids during periods of possible stress.
- Physician consultation.

Mineralocorticoid

The natural mineralocorticoids are

- Aldosterone
- Deoxycorticosterone

Physiological actions

Aldosterone acts on the Distal convoluted tubule and the collecting duct and increases the reabsorption of sodium ions.

An increase in extra-cellular fluid volume and blood volume finally leads to an increase in blood pressure.

Increase in the potassium excretion through the renal tubules.

Therapeutic Uses

- Salt losing congenital adrenal hyperplasia.
- Hyporenenimic hypoaldosteronism.
- Severe postural hypotension.
- Dosage: 0.05-0.30 mg daily in adults.

Tests to detect corticosteroid activity in the body

- Adrenal function tests
- **Acth stimulation test**

  "A plasma Cortisol level of 18 Mcg% or higher, one hour after an IV bolus injection of Tetracosactrin .....250 mcg indicates normal adrenocortical function."
- **Dexamethasone suppression test**

  "Plasma Cortisol level is measured the morning after administration of 1 Mg of Dexamethasone orally at 10 p.m. A level of less than 5 mcg% indicates normal suppression."

Conclusion

"Practitioners must keep in mind that the judicious use of corticosteroids is both satisfying and life-saving for the patient, By acting as the final and best option in reducing the chronicity of the illness and even in complete elimination of the disease despite their well-known adverse effects so thorough knowledge and clinical implications should be well known while prescribing these medical agents which plays a very crucial in the overall wellbeing of the patient"

Conflicts of Interests

There are no conflicts of interest in this article.

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