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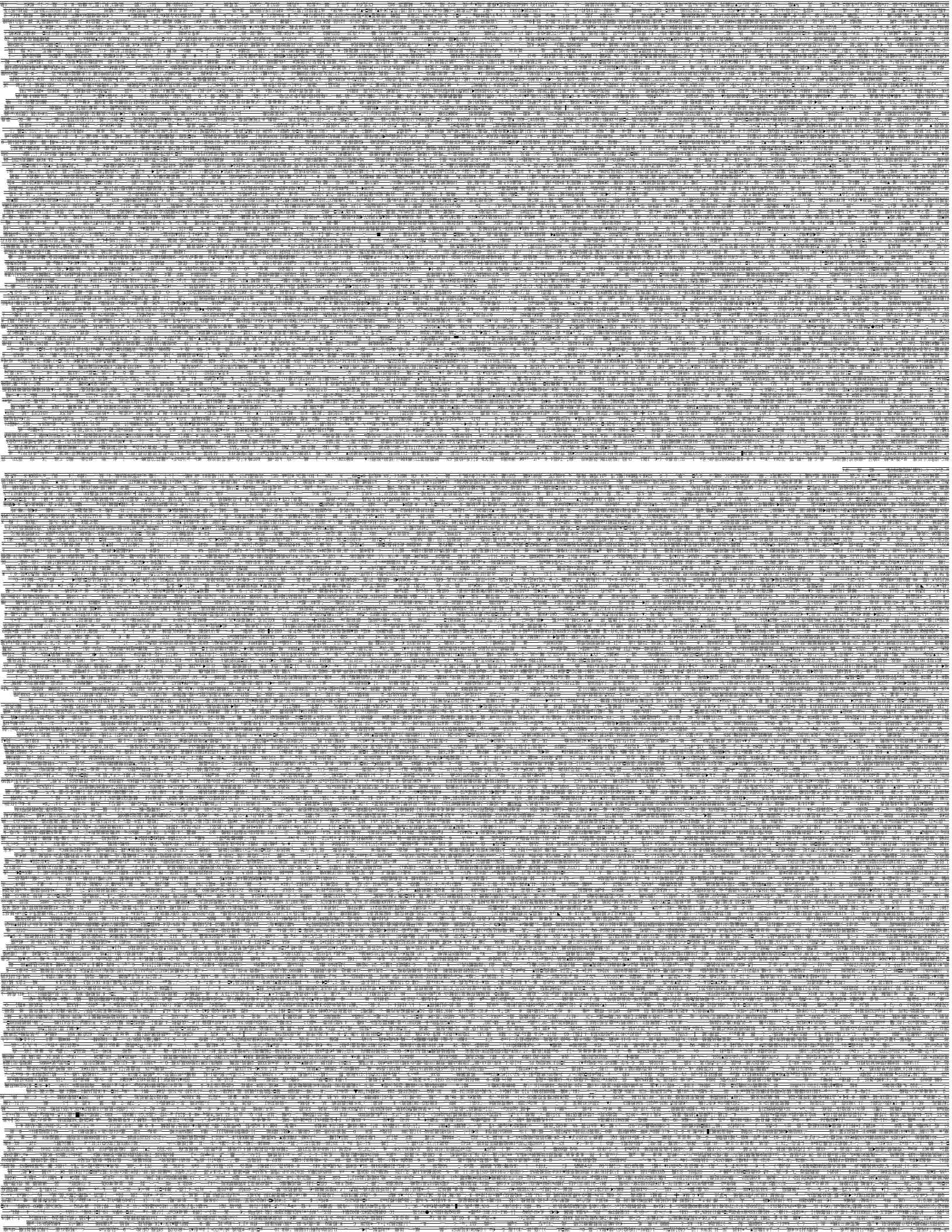

Agents used in endocrine system

Some endocrine hormones and relative drugs

1.adrenocorticoids 2.Posterior pituitary hormones 3.insulin and oral hypoglycemic agents 4.thyriod and anti-thyriod drugs

Adrenal Gland

Endocrine Glands

Adrenocortical hormones

Adrenocortical hormones are all the hormones that are secreted by adrenal.

Adrenal Gland

Actually 2 glands Each portion has different functions and secretes different hormones

Adrenal Gland

Adrenal medulla: secretes: Epinephrine(AD) Norepinephrine(NE) Adrenal cortex: secretes corticosteroids All adrenal cortex hormones are steroid hormones

Adrenal cortex

Composed of 3 layers (zones) outer zone (zona glomerulosa) produces mineralocorticoid (eg.aldosterone) middle zone (zona fasciculata) produces glucocorticoids (eg.cortisol) inner zone (zona reticularis) produces some sex hormones

Adrenal regulation

HPA (hypothalamic-pituitary-adrenal cortex) axis

Hypothalamus pituitary adrenal cortex

(Glucocorticoids GCS

Structure-activity relationship of adrenocortical hormones

C17: OH C11= O or OH are necessary for GCs. C1 2= Antiinflammatory effects stronger, effects of water-electrolyte metabolism weaker

C9: F C16: CH3 or OH Antiinflammatory effects stronger, effects of water-electrolyte metabolism weaker.

[Pharmacokinetics] Absorption: orally or injection. Distribution:In plasma,77% of GCS is Bound to corticosteroid binding Globulin(CBG or transcortin), 10% is Bound to albumin, the remainder if free. Estrogen CBG Heptic disease CBG

Elimination: metabolized in liver C4-5 and C3=0 were reduced. Excretion: urine cortisone and prednisone can be separately converted into hydrocortisone and prednisolone, Then produce the effects. (in severe heptic disease, only hydrocortisone and prednisolone can be used)

physiological effects

At doses corresponding to normal daily production level, it was viewed as physiological effects. In physiology dose, GCS mainly affects normal metabolism, including substance metabolism and water /salt metabolism

Effects on metabolism

1. Effects on carbohydrate metabolism: the blood glucose level stimulate glucose production from amino acid and glycerol :glyconeogenesis a stimulate glycogen deposition in liver b decrease the oxidation and utilization of glucose by inhibiting the Carrier transport in peripheral tissues. the net result: hyperglycemia, may induce DM.

physiological effects

2.Effects on protein metabolism stimulate protein degradation a inhibit protein synthesis net result: negative nitrogen balance can lead to decreased muscle mass and weakness.

physiological effects

3. Effects on fat metabolism: promote the lipolysis in lipocytes. a cause dramatic redistribution of body fat. Result: concentric obesity (a special shape: moon shaped face, trunk obesity)

concentric obesity

physiological effects

4. Effects on salt and water balance : they have weak mineralocorticoids-like activity , which may lead to water and sodium retention, hypokalemia, hypocalcemia and osteoporosis 5) Nucleic acid metabolism

1. Permissive action (in stress state) GCs facilates other hormonal effects other than direct effects.

Pharmacological effects

At doses exceeding the normal daily production of glucocorticoids, it was viewed as pharmacological effects. four anties and other effects anti-inflammatory effects anti-immune effects antitoxic effects anti-shock effects

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anti-inflammatory effects: Characteristics: rapid, strong , nonspecific , both the early phase and late phase

symptoms of early phase inflammation: redness, edema, fever , pain; During the early phase of inflammation, improve symptoms by inhibiting capillary ectasia, permeability, exudation and edema and the infiltration and phagocytose of leucocytes.

symptoms of later phase inflammation: the formation of cohesion and scar inflammatory sequela. During the late phase of inflammation, prevent the formation of cohesion and scar by inhibiting the proliferation of capillary and fibroblast, delaying the formation of granulation tissues, and reduce the sequelas of inflammations.

anti-inflammatory effects:

The suppression of inflammation is of great clinical use. Because of this, these drugs were the most frequently prescribed agents in clinic. Note : The use of glucocorticoids does not aim directly the underlying cause of the disease, sometimes they may lead the infections to get worse by reducing the immunologic function of the patients. When it was used to treat infections, it must combine with enough effective antibiotics.

Mechanism of anti-inflammatory action

GCS diffused into cytoplasm,then combine with complex of GR-HSP. Then HSP is released, GR complex is transported into nucleus, then combined with GRE or nGRE, then influence gene transcription of some cytokine.

Mechanism of anti-inflammatory action

1.Regulating the production of cytokine, reducing the cell response of inflammation : GCS can inhibit the production of some pro-inflammatory cytokine(IL-1, IL-3, IL-8, TNF-) and can induce the production of some anti-inflammatory cytokine(IL-10).

Mechanism of anti-inflammatory action

2.Affecting the metabolism of AA arachidonic acid and decreasing the productions of PGs and LTs (Leukotrienes).

Mechanism of anti-inflammatory action

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Mechanism of anti-inflammatory action

4.Inducing ACE (angiotensin converting enzyme), and accelerating the degradation of BK (bradykinin) ACE BK degradation product

immunosuppressive effects

Inhibiting phagocytosis and management of macrophages on antigen promoting the redistribution of lymphocyte in human blood, decreasing the number of lymphocytes in circulation inhibiting the cell immunity in small dose, inhibiting the humoral immunity in large dose Antibody production can be reduced by large doses of GCS. Because GCS inhibit the proceeding that B cell converted into plasma cell. In additon,GCS stabilize mast cell membrane.

antitoxic effects :in very large dose

GCS have no effects on exotoxin, and can not neutralize endotoxin either. It can enhance the tolerance of our body to bacterial endotoxin, thus have rapid antipyretic and antitoxic effects.

anti-shock effects: in Super large dose

(especially infectious-toxic shock Mechanism: relaxing the smooth muscle of spasmodic vessels and enhancing the contractility of myocardium reducing the sensitivity of some vasoconstrictive substances on vessel stabilizing the lysosomal membrane and decreasing the production and release of MDF (myocardial-depressant factor) enhancing tolerance of body on bacterial endotoxins

effects on blood and hemopoietic system

stimulate hemopoiesis: increase the number of RBC, PLT, and Hb(hemoglobin) in circulation. Increase the number of neutrophils but inhibiting their function Reduce the number of other blood cells, such as lymphocytes , monocytes , eosinophils and basophils in blood.

other effects

Central nervous system: GCS can stimulate the CNS and may cause euphoria, excitement insomnia, and insomnia, euphoria, inducing psychosis and epilepsy. Digestive system: GCS can stimulate the secretion of pepsin and gastric acid, and may induce peptic ulcer. Skin and bone (osteoporosis)

Clinical uses

1.replacement therapy: in small dose acute or chronic hypofunction of adrenal cortex for example. Addison s disease Adrenal insufficiency can result from structural or functional lesions of the adrenal cortex itself (primary adrenal insufficiency) or of the anterior pituitary or hypothalamus (secondary adrenal insufficiency)

HPA (hypothalamic-pituitary-adrenal cortex) axis

R Seconary Hypothalamus pituitary Primary :adrenal cortex

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4.Shock

GCS are effective to all kinds of shock, They are the first choice in the treatment of infectious-toxic shock. And can also be used as supplements to treat anaphylactic shock, cardiogenic shock , hypovolemic shock and so on.

5.Other clinical uses

(1)Blood disorders Acute lymphatic leukemia, aplastic anemia (AA), thrombocytopenia, granulocytopenia (2)Use of local therapy topical uses some skin diseases some eye disease

Adverse reactions

Adverse reactions caused by continuous and longtime use of large doses of GCS Withdrawl reactions: adverse reactions caused by sudden withdrawl after a continuous and longtime use

Adverse reactions caused by continuous and longtime use of large doses of GCS

1) Iatrogenic Cushing s syndrome mainly caused by metabolism disorder of lipid, protein, glucose and water&salt. The symptoms include moon shaped face, trunk obesity,thin skin,sodium retention, hypokalemia,edema, pilosity, hypertension, acne,diabetes, muscle wasting . prednisone: 20mg/d , last for 1 month

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(Results from too rapid withdrawl of GCS after prolonged therapy) Iatrogenic adrenocortical insufficiency : adrenocortical atrophy and adrenal crisis Mechanism: the HPA (hypothalamic-pituitary-adrenal cortex) axis is suppressed

Mechanism: the HPA axis is suppressed

Too much GCS in the plasma can inhibit the release of ACTH and CRH due to negative feedback. And it ll take a long time for the pituitary and hypothalamus to recover function. Many patients recover from GCS -induced HPA suppression within several weeks to months. However, in some individuals, the time to recovery can be one year or longer. To avoid such kind of adverse reaction, when GCS dose need to be stopped after a long time use, we should decrease the dose slowly.

the HPA (hypothalamic-pituitary-adrenal cortex) axis

Hypothalamus pituitary adrenal cortex

Hypothalamus

Adrenal crisis:nausea,vomiting, weakness,hypotension, hypoglycemia,shock. 2 Rebound phenomenon [Contraindications]

Generally speak,severe psychosis and epilepsy,active peptic ulcer,fracture,corneal ulcer, severe hypertension,diabetes, pregnancy [Method of application] 1) Impact (emergency) therapy with large dose

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Section 2 Corticotropin (adreno-cortico-tropic hormone,ACTH) and inhibitors of cortical hormones. 1) ACTH 2) Ihibitors of cortical hormones mitotan metyrapone

Section3 Mineralocorticoids aldosterone, desoxycortone

Steroid nucleus is a basic structure C3 = 0 C4-5 C20 =0 are necessary

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PPT10 PPT10

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H2.Effects on inflamatory factor and target enzyme 1)Affecting the metabolism of AA arachidonic acid and decreasing the productions of PGs and LTs (Leukotrienes).
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j4.Induce apoptosis of inflamatory cel Caspase(JS)
la! . immunosuppressive effects and anti-alergic effects
1. immunosuppressive effects 1)Inhibiting phagocytosis and management of macrophages on antigen 2) promoting the redistribution of lymphocyte in human blood, decreasing the number of lymphocytes in circulation
na! . immunosuppressive effects and anti-alergic effects
3)inhibiting the cell immunity in small dose, inhibiting the humoral immunity in large dose 4)Antibody production can be reduced by large doses of GCS. Because GCS inhibit the proceeding that B cell converted into plasma cell. 5)In additon,GCS stabilize mast cell membrane.
2. anti-alergic effects Inhibit antigen-antibody effect 0000000 ! degranulation of mast cell
Nb! antitoxic effects :in very large dose
GCS have no effects on exotoxin, and can not neutralize endotoxin either. It can enhance the tolerance of our body to bacterial endotoxin, thus have rapid antipyretic and antitoxic effects.
Vc!. anti-shock effects: in Super large dose
especially infectious-toxic shock Mechanism: 1) relaxing the smooth muscle of spasmodic vessels and enhancing the contractility of myocardium 2) Inhibiting production of some inflamatory factor and reducing the sensitivity of some vasoconstrictive substances on vessel 3) stabilizing the lysosomal membrane and decreasing the production and release of MDF (myocardial-depressant factor) 4) enhancing tolerance of body on bacterial endotoxins
Xd!. effects on blood and hematopoietic system
stimulate hemopoiesis: increase the number of RBC, PLT, and Hb(hemoglobin) in circulation. Increase the number of neutrophils but inhibiting their function Reduce the number of other blood cells, such as lymphocytes , monocytes , eosinophils and basophils in blood.
"e! . other effects
1. Central nervous system: GCS can stimulate the CNS and may cause euphoria, excitement insomnia, and insomnia, euphoria, inducing psychosis and epilepsy. this effect is related to reduction of GABA concentration in CNS.
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2) virus infection But we usually not use GCS to treat infections of virus except severe infective hepatitis , epidemic parotitis , measles and encephalitis. But not used for long-time. (varicella, herpes zoster no use of GCS). (2) Pervent some inflammatory equela ! scar and cohesion Tuberculous meningitis, tuberculous pleuritis, pericarditis, ocular diseases:iritis,keratitis, retinitis. Testitis, traumatic arthritis "3.Allergic and autoimmune diseases F1.Allergic diseases: Bronchial asthma, urticaria, hay fever, anaphylactic rhinitis. Angioneuro-edema, allergic shock anti-histamines(H1-R antagonists) are the drugs of first choice. adequate doses of GCS can be given as supplements to the primary therapy. 2. Autoimmune diseases: used widely (first choice) Rheumatic fever,rheumatic or rheumatoid arthritis,rheumatic myocarditis,systemic lupus erythematosus,dermatomyositis, autoimmune hemolytic anemia, nephrotic syndrome, allotransplantation of organs 4.Shock GCS are effective to all kinds of shock. They are the first choice in the treatment of infectious-toxic shock. And can also be used as supplements to treat anaphylactic shock, cardiogenic shock , hypovolemic shock and so on. 5.Other clinical uses (1)Blood disorders Acute lymphatic leukemia, aplastic anemia (AA), thrombocytopenia, granulocytopenia (2)Use of local therapy topical uses some skin diseases some eye disease Adverse reactions Adverse reactions caused by continuous and longtime use of large doses of GCS Withdrawl reactions: adverse reactions caused by sudden withdrawl after a continuous and longtime use 1) Iatrogenic Cushing s syndrome mainly caused by metabolism disorder of lipid, protein, glucose and water&salt. The symptoms include moon shaped face, trunk obesity,thin-skin,sodium retention, hypokalemia,edema, pilosity, hypertension, acne,diabetes, muscle wasting . prednisone: 20mg/d , last for 1 month 2) Induction and aggravation of infection: Note: GCS should be administered only if absolutely necessary and must be used plus enough effective antibacterial agents 3) Possible risk of peptic ulcers Treatment: a. lower doses b. avoid combinated use with other mucose-injury drugs 4) Cardiovascular complications hypertension atherosclerosis 5) Other complications a. Osteoporosis b. psychosis, euphoria c. growth retardation 2.Withdrawal reactions (Results from too rapid withdrawl of GCS after prolonged therapy) 1) Iatrogenic adrenocortical insufficiency : adrenocortical atrophy and adrenal crisis Adrenal crisis: nausea,vomiting,weakness, hypotension, hypoglycemia, shock. Mechanism: the HPA axis is suppressed Too much GCS in the plasma can inhibit the release of ACTH and CRH due to negative feedback. And it ll take a long time for the pituitary and hypothalamus to recover function. Many patients recover from GCS-induced HPA suppression within several weeks to months. However, in some individuals, the time to recovery can be one year or longer. To avoid such kind of adverse reaction, when GCS dose need to be stopped after a long time use, we should decrease the dose slowly. 5the HPA (hypothalamic-pituitary-adrenal cortex) axis Hypothalamus pituitary adrenal cortex Rebound phenomenon [Contraindications] severe psychosis and epilepsy,active peptic ulcer,fracture,corneal ulcer, severe hypertension, diabetes, pregnancy [Method of application] 1) Impact (emergency) therapy with large dose 2) Long-term therapy with moderate dose 3) Substitution therapy with small dose 4) Therapy on every other day Attention items: Section 2 Mineralocorticoids aldosterone desoxycortone Section 3 Corticotropin (adreno-cortico-tropic hormone,ACTH) and inhibitors of cortical hormones. 1) ACTH 2) Inhibitors of cortical hormones mitotan metyrapone

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Distribution in plasma,77% of GCS is Bound to corticosteroid binding Globulin(CBG or transcortin), 10% is Bound to albumin, the remainder if free. Estrogen CBG Heptic disease CBG Elimination: metabolized in liver C4-5 and C3=O were reduced. ! cortisone and prednisone can be separately converted into hydrocortisone and prednisolone. Then produce the effects. (in severe heptic disease, only hydrocortisone and prednisolone can be used) Excretion: urine physiological effects At doses corresponding to normal daily production level, it was viewed as physiological effects. In physiology dose, GCS mainly affects normal metabolism, including substance metabolism and water /salt metabolism Effects on metabolism 1. 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