Androcortil®

hydrocortisone sodium succinate

SIMILAR MEDICINAL PRODUCTS EQUIVALENT TO MEDICINAL PRODUCTS REFERENCE

PRESENTATIONS

Lyophilized powder solution for injection 100mg
Package containing 50 vials.

INTRAVENOUS OR INTRAMUSCULAR USE
ADULT AND PEDIATRIC USE

COMPOSITION
Each 100mg vial contains:
lyophilized buffered hydrocortisone sodium succinate* (equivalent to 100mg hydrocortisone) 134mg

* Buffer component: disodium phosphate.

TECHNICAL INFORMATION FOR HEALTHCARE PROFESSIONALS

1. INDICATIONS
Androcortil® is indicated for the treatment of:
- endocrine disorders such as primary acute adrenal insufficiency (Addison's disease) or secondary, primary or secondary secondary adrenal insufficiency in patients undergoing stressful situations (surgery, infections, labor) and thyrotoxic crisis;
- rheumatological and autoimmune diseases;
- anaphylaxis;
- asthma;
- septic shock;
- ulcerative colitis;
- migraine;
- post-cardiac surgery;
- infliximab pre-infusion;
- trauma patients;
- maturation of the fetal lung.

2. EFFICIENCY RESULTS
Acute adrenal insufficiency
Bouillon, in a review of acute adrenal insufficiency, mentions that the adrenal crisis treatment is relatively straightforward, consisting of replacement hydroelectrolytic and hydrocortisone. After confirmation of the diagnosis, replacement should be instituted intravenously or intramuscularly, at doses of 150 to 300mg daily for 2 or 3 days, until complete clinical recovery. At this dose, considered a dose of physiological stress, hydrocortisone exerts mineralocorticoid effects, by activating mineralocorticoid receptor and therefore no additional mineralocorticoid therapy is required.[1]
Falorni and colleagues recently published an update on adrenal insufficiency, drawing attention to the fact that the adrenals are glands activated during stress to increase cortisol secretion. Therefore, the glucocorticoid replacement doses should be increased in situations of infection, trauma or surgical interventions.[2]

Septic shock
In the 1990s, three small studies showed that, compared to placebo, low doses of hydrocortisone (eg 200 to 400mg) in patients with shock septic resulted in faster reversion of shock (withdrawal of vasopressor drugs); these studies have encouraged larger randomized clinical trials. At the first multicentre, double-blind study conducted in France, 300 patients with septic shock dependent on vasopressor drugs were randomized to receive placebo or hydrocortisone (50mg intravenous every 6 hours) plus fludrocortisone (50µg enterally once a day). Based on an ACTH stimulus test, patients were classified as having an adequate adrenal reserve (increased maximum cortisol> 9µg / dL) or inadequate (maximum cortisol increase ≤ 9µg / dL).
Considering all patients, hydrocortisone reduced mortality in 28 days (55% versus 61%). Among patients with inadequate adrenal reserve, hydrocortisone decreased mortality in 28 days (53% versus 63%), mortality in the therapy unit intensive (58% versus 70%) and hospital mortality (61% versus 72%).
In the second multicentric study (Corticosteroid Therapy of Septic Shock, CORTICUS), randomized, double-blind and placebo controlled study, 499 patients with septic shock were treated with hydrocortisone (50mg) or intravenous placebo every 6 hours for 5 days, followed by a gradual withdrawal regime. Patients were again classified as having an adequate or inadequate adrenal reserve. The administration of hydrocortisone did not improve mortality in 28 days (35% versus 32% in the group placebo), but determined a faster reversal of shock in all patients (3.3 versus 5.8 days in the placebo group).
Based on these results, the evidence-based medicine website UpToDate® recommends the use of glucocorticoids, specifically hydrocortisone, in the treatment of refractory septic shock, at a dose of 200 to 300mg per day, intravenously, in doses divided (50mg every 6 hours or 100mg every 8 hours), without adding fludrocortisone, since hydrocortisone alone already has an effect sufficient mineralocorticoid. The recommended duration is 5 to 7 days and the withdrawal depends on the clinical response, for example, a quick withdrawal can be performed after withdrawal of vasopressor drugs or a slower withdrawal may be preferred if there is a coexisting indication, such as, for example, a picture of exacerbation of chronic obstructive pulmonary disease (COPD).[3]
A meta-analysis published in JAMA examined the benefits and risks of treatment with glucocorticoid in the treatment of septic shock. In general, glucocorticoids did not affect all-cause mortality in 28 days, however, a meta-analysis of a subgroup of 12 studies that investigated the prolonged use of low doses of glucocorticoids suggested a favorable effect on all-cause mortality. In according to these findings, glucocorticoids should be considered in the daily dose of 200 to 300mg of hydrocortisone (or equivalent) as an intravenous bolus or infusion to be continued. The authors suggest that the treatment be administered for at least 100 hours in adults with vasopressor drug-dependent septic shock.[4]

Anaphylaxis
The effectiveness of glucocorticoid administration in anaphylaxis has never been determined in placebo-controlled clinical studies. However, its usefulness in other diseases allergic reactions led to the incorporation of these drugs in the treatment of anaphylaxis. An since the onset of action of glucocorticoids is not immediate, they are not useful in the management acute stage, but it is suggested that its use may prevent biphasic reaction, reason why anaphylaxis treatment algorithms recommend the use of glucocorticoids in the management of this clinical condition.[5]
As can be seen in the Guidelines of the Working Group of the Board of Resuscitation (Working Group of the Resuscitation Council, a group of experts students dedicated to the study and education of health professionals and the lay public appropriate methods of resuscitation), hydrocortisone is one of the glucocorticoids that can be used to treat anaphylaxis.[6]

Thyrotoxic crisis
The therapeutic regimen typically consists of multiple medications, each with a different mechanism of action: a beta blocker to control symptoms and signs induced by increased adrenergic tone; a thionamide (propiotiouracil or methimazole) to block the synthesis of thyroid hormones; an iodine solution to block the release of thyroid hormones; iodinated contrast (if available) to inhibit the peripheral conversion of T4 to T3 and glucocorticoids to reduce the conversion of T4 to T3, promote vasomotor stability and possibly treat an insufficiency relative adrenal gland. Additionally, glucocorticoids can have a direct effect on the underlying autoimmune process if the thyrotoxic crisis is due to Graves' disease.
The use of glucocorticoids in the treatment of thyrotoxic crisis improved the results of the treatment in at least a series of patients and, therefore, it is recommended to administration of hydrocortisone 100mg every 8 hours intravenously in the treatment this clinical emergency.[7]

Asthma
Krishnan and colleagues summarized the state of knowledge about the use of glucocorticoids in patients with acute asthma, systematically reviewing the Library Cochrane and additional clinical studies published in English from 1966 to 2007.
The findings of this review suggest that systemic glucocorticoid therapy accelerates the resolution of acute asthma symptoms and reduces the risk of recurrence. There is no evidence that doses higher than the standard doses are beneficial. Glucocorticoid regimens oral and intravenous or intramuscular and oral were similarly effective. The hydrocortisone at a dose of 250-500mg intravenously in a single daily dose is one of the glucocorticoid options to be used in the treatment of acute asthma in patients adults.[8]
In an article published in 2010, the Canadian Thoracic Society summarized the key messages for the non-ventilatory treatment of acute asthma from a wide range search on the PubMed website, same as that used by the Global Initiative for Asthma group, in addition to research in other databases, such as the Cochrane Library and EMBASE, for example. Hydrocortisone at a dose of 250 or 500 mg intravenously is recommended in the treatment of severe asthma.[9]

Rheumatological diseases
Glucocorticoids have been the cornerstone of rheumatological diseases for many decades and there is detailed information about the capacity of this class of medicines to slow the progression of joint damage in rheumatoid arthritis. The glucocorticoids are also used, often in larger doses, in the treatment other rheumatological diseases, such as polymyalgia, systemic lupus erythematosus and vasculitis.
The EULAR (The European League Against Rheumatism) recently developed recommendations for the management of medium to high doses of glucocorticoids (equivalent doses> 7.5mg, but ≤ 100mg of prednisone daily) in the treatment of diseases rheumatological disorders. Its objective was to formulate 10 recommendations on the management of doses and elevated levels of glucocorticoids for the identification and critical analysis of studies available in the literature.
In the item that addressed the management of suppression of the induced hypothalamus-pituitary-adrenal by treatment with glucocorticoids, experts drew attention to the risk of adrenal insufficiency in those patients in whom the use of glucocorticoids is abruptly stopped and in acute stress situations and that, therefore, will need glucocorticoid supplementation during the stress period. Although the susceptibility to suppression of the hypothalamus-pituitary-adrenal may vary from one person to another, it should be expected in patients receiving equivalent doses prednisolone> 7.5mg for a period longer than 3 weeks. Therefore, it is recommended to adequate glucocorticoid replacement in patients receiving medium and high doses of glucocorticoids exposed to acute complications. The recommendation is that the doctor of this patient choose to increase the dose of glucocorticoid that the patient is making use of it, or to exchange the orally administered glucocorticoid for intravenous hydrocortisone, started, for example, at a dose of 25mg, twice a day, to patients receiving 10mg of prednisolone daily, or 50mg, 3 times daily, for those patients receiving higher doses of glucocorticoids.[10]

Autoimmune hepatitis
According to the British Gastroenterology Society Guidelines, developed on the basis of published evidence (including from the American Association for the Study of Liver Disease, AASLD), the initial treatment of autoimmune hepatitis should be done prednisolone (initially at a dose of 30mg / day, with a reduction to 10mg / day at over 4 weeks) plus azathioprine (1mg / kg / day).
In 80 to 90% of patients with moderate to severe disease, serum concentrations of aminotransferases fall after starting treatment, usually in approximately 2 weeks. In patients who do not respond or respond very slowly and do not liver failure, prednisolone can be increased to 60mg / day and azathioprine to 2mg / kg / day, if tolerated.
The British Society of Gastroenterology guidelines recommend that, if there is possibility of non-adherence to therapy or malabsorption, the patient must be hospitalized and treated with parenteral GCs, such as intravenous hydrocortisone or methylprednisolone.[11]

Severe ulcerative colitis
Initial therapy for patients with severe ulcerative colitis should include glucocorticoids oral and combined high-dose oral therapy of 5-amino-salicylic acid (5-ASA), for example, mesalamine. Those patients who have fever and leukocytosis should receiving antibiotics and malnourished patients must receive nutritional support.
Patients who continue to show symptoms despite optimal doses of glucocorticoids and high doses of 5-ASA should be hospitalized to receive replacement
hydroelectrolytic and intravenous glucocorticoids, which include prednisolone (30mg a every 12 hours), methylprednisolone (16 to 20mg every 8 hours) or hydrocortisone (100mg every 8 hours).[12]

Migraine status
The American Academy of Neurology has established evidence-based Guidelines for the treatment of migraine. The section on acute treatment describes the following group of drugs:
- other medicines: this group includes isometepten and combinations of isometepten-containing agents as treatment options for headache patients mild to moderate and glucocorticoids (dexamethasone and hydrocortisone) for treatment of migraine status.[13]

Prevention of atrial fibrillation after cardiac surgery
Glucocorticoids are potent inhibitors of the inflammatory cascade and limit the increase interleukin (IL) -6 (IL-6), IL-8, tumor necrosis factor alpha (TNF-α), PCR and species reactive oxygen after cardiopulmonary bypass. This anti-inflammatory effect is associated with reduced kidney damage, improved myocardial function and increased number of days without the use of ventilators, with a reduction in the length of hospital stay in intensive care units. Therefore, it is suggested that by inhibiting the pro-response inflammatory reaction after cardiopulmonary bypass, administration of glucocorticoids in the perioperative period could decrease the incidence of fibrillation post-surgical atrial Marik and colleagues conducted a systematic review to assess the role of glucocorticoids in the prevention of atrial fibrillation in patients undergoing surgery cardiac. Therefore, they collected data related to the experimental design, type of study and surgery, glucocorticoid dose regimen and the incidence of atrial fibrillation in the first 72 hours after the surgical procedure. The cumulative dose of glucocorticoid was classified as low (<200mg / day), moderate (200-1000mg / day), high (1,001-10,000mg / day) or very high (10,000mg / day) of equivalents of hydrocortisone.
A total of 7 relevant studies that included 1,046 patients were identified, in the which different glucocorticoid regimens were used, with cumulative doses ranging from 160 to 21,000 mg of hydrocortisone equivalents. In general, the use of glucocorticoids were associated with a significant reduction in the risk of post-atrial fibrillation surgery, with an odds ratio (OR) of 0.42, a 95% confidence interval (CI) of 0.27 - 0.68 and a value of P = 0.0004. With the exclusion of low doses and very high doses, the treatment effect was highly significant (OR 0.32; 95% CI 0.21 - 0.50; P < 0.00001). There were no complications associated with the use of glucocorticoids.
The result of this meta-analysis suggests that the use of glucocorticoids in the period surgery reduces the risk of post-surgical atrial fibrillation to a greater extent than 50%, with or without the concomitant use of beta-blockers. However, the effect seems dependent on the dose regimen used, since both very high doses and low glucocorticoids were ineffective, unlike moderate and high doses, which were effective. Thus, cumulative doses less than 200mg of hydrocortisone are insufficient to adequately suppress the systemic inflammatory response associated with Cardiac surgery. On the other hand, very high doses of glucocorticoids may have deleterious effects, perhaps by altering membrane phospholipids and thus affecting the flow of potassium across the cell membrane and promote arrhythmias. It has already been demonstrated that high doses of methylprednisolone are associated with the appearance of atrial fibrillation.
Thus, the pro-arrhythmogenic effect of very high doses of glucocorticoids can nullify the beneficial anti-inflammatory effects.
The authors concluded that moderate doses of glucocorticoids (between 200-1,000 mg / day hydrocortisone) should be considered for the prevention of atrial fibrillation in high-risk patients undergoing cardiac surgery.[14]

Multiple trauma
Administration of hydrocortisone doses to improve the stress response in septic shock patients with relative adrenal insufficiency (associated with the disease critical) is reasonably well established. In addition, an inflammatory response persistent infection was predictive of nosocomial infection in patients with trauma and trauma-related adrenal gland also correlated with the response syndrome systemic inflammatory disease. It has been suggested that hydrocortisone attenuates the response marked inflammatory response, restoring an adequate immune response without causing immunosuppression. Due to this reason, Roquilly and colleagues postulated that treatment of trauma patients with doses of hydrocortisone that improve response to stress could decrease the prevalence of hospital-acquired pneumonia, which is the leading cause of infection in these patients and conducted a multicenter study, randomized, double-blind, placebo-controlled study called HYPOLYTE (Hydrocortisone Polytraumatise). A total of 150 patients with severe trauma and for which the need for mechanical ventilation for more than 48 hours was expected was included in 7 intensive care units in France and patients were randomized to receive the continuous intravenous infusion of hydrocortisone (200mg / day for 5 days, followed by 100mg on the 6th day and 50mg on the 7th day) or placebo. Patients with insufficiency adrenal gland or using glucocorticoids in the 6 months prior to inclusion were excluded.
The infusion of the study drug (hydrocortisone sodium succinate or placebo) started within 36 hours of the trauma, immediately after performing a stimulus test with ACTH. Glucocorticoid insufficiency was defined in basal cortisol concentration <15µg / dL or a maximum increase in concentration cortisol <9µg / dL 60 minutes after ACTH injection. Treatment was interrupted in those patients who had an appropriate cortisol response. The outcome main study was hospital-acquired pneumonia at 28 days and the outcomes side effects included the duration of mechanical ventilation, hyponatremia and mortality.
The intention-to-treat (ITT) analysis included 149 patients and the ITT analysis.
The modified procedure included only 113 patients with adrenal insufficiency. In the ITT analysis 35.6% of patients treated with hydrocortisone and 51.3% of patients treated with hydrocortisone placebo developed hospital pneumonia in 28 days (RR 0.51; 95% CI 0.30 - 0.83; P = 0.007). In the modified ITT analysis, the frequency of hospital-acquired pneumonia in 28 days was 35.7% and 54.4%, respectively (RR 0.47; 95% CI 0.25 - 0.86; P = 0.01). Significant differences were also observed between the two groups in the outcomes side effects, in favor of sodium hydrocortisone succinate, except for mortality, that did not reach a significant difference between the two groups.
Among patients with adrenal insufficiency, norepinephrine was discontinued earlier in the group receiving hydrocortisone than that receiving placebo, possibly because hydrocortisone raises blood pressure, increases vascular tone and increases endothelial reactivity to vasopressors.
The authors concluded that a physiological dose of hydrocortisone stress during 7 days was associated with a 28-day reduction in the rate of nosocomial pneumonia, together with a decrease in the need for mechanical ventilation and length of stay in the intensive care unit in patients with multiple traumas.[15]

Infliximab pre-infusion
Infliximab, a chimeric monoclonal antibody (part murine and part human) directed against TNF-α represented an important advance in the treatment of Crohn's disease refractory to treatment.
As immunogenicity could be a problem in the use of infliximab over the long term Farrell and colleagues evaluated the relationship between anti-infliximab antibodies and loss of response to therapy, as well as the frequency of infusion reactions, in one study clinical trial in which hydrocortisone was used as premedication before the infusion of infliximab.
Initially, the authors prospectively assessed the clinical response, events adverse reactions and anti-infliximab antibody titers in 53 consecutive patients with Crohn's disease who received 199 infusions of infliximab (5mg / kg). Next, 80 Crohn's disease patients were randomized to receive hydrocortisone 200 mg or placebo immediately before the first infusion and subsequent infusions. The primary outcome was a reduction in median anti-infliximab antibodies at week 16. The analysis was performed with the intention of treatment (ITT).
Nineteen of the initial 53 patients (36%) developed anti-infliximab antibodies, including the 7 patients who had serious infusion reactions. Eleven of 15 patients (73%) who lost their initial response had positive antibodies in compared to none among 21 patients who continued to respond to infliximab.
In the placebo-controlled study, anti-infliximab antibody titers were more low at week 16 in patients treated with hydrocortisone (1.6 versus 3.4µg / mL, P = 0.02) and 26% of patients treated with hydrocortisone developed antibodies in compared to 42% of patients in the placebo group (P = 0.06).
The authors concluded that loss of initial response and infusion reactions are strongly related to formation and with the titles of anti-infliximab antibodies. Intravenous hydrocortisone administered as premedication significantly reduces the formation of antibodies and the frequency of infusion reactions.[16]
The use of a single dose of 100mg of hydrocortisone 20 minutes before the infusion of infliximab is recommended as one of the glucocorticoid options for prophylaxis infusion reactions.[17]

Induction of fetal lung maturation
In 1972, Liggins and Howie demonstrated that a single course of therapy with antenatal glucocorticoids administered to women at risk of preterm delivery reduced the incidence and severity of respiratory distress syndrome and the mortality of newborns born. After that, numerous clinical studies confirmed these findings and additionally demonstrated that glucocorticoid therapy improves stability circulation, resulting in less ventricular hemorrhage and less enterocolitis necrotizing compared to premature neonates not exposed to glucocorticoids.
The National Institute of Health, the American College of Obstetrics and Gynecology, the Royal College of Medicine and other important organizations recommend treatment antenatal with glucocorticoids for women at risk of preterm delivery before 34 ° week of gestation to reduce morbidity and mortality associated with prematurity.
Moore and Martin conducted a literature review to evaluate other glucocorticoids maturation of the fetal lung and found 8 studies carried out between 1966 and 2001. After betamethasone and dexamethasone, glucocorticoids most often studied for this indication were methylprednisolone and hydrocortisone. The methylprednisolone had no impact on lung maturation, whereas studies Hydrocortisone showed that it has a faster onset of action and shorter half-life than betamethasone and thus a shorter period of action on the fetal lung. These authors concluded that hydrocortisone appears to be the most effective when betamethasone and dexamethasone are not available.[18]
Based on these results, the evidence-based medicine website UpToDate® recommends the use of hydrocortisone at a dose of 500mg intravenously every 12 hours by 4 doses as a last resort, in the case of betamethasone and dexamethasone not be available.[19]

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3. PHARMACOLOGICAL CHARACTERISTICS

Pharmacodynamic properties

Mechanism of action

Similar to cortisol, hydrocortisone sodium succinate exerts its effects after binding to glucocorticoid receptors (GR) present in the cell cytoplasm. The hormone-receptor complex translocate to the nucleus, where it modifies transcription directly by binding to glucocorticoid-responsive elements (GRE) located in the promoter region of the target genes, or indirectly, interacting with other transcription factors, such as activator protein-1 (AP-1) and the pro-factor inflammatory NF-kB, preventing them from having access to their binding sites in deoxyribonucleic acid (DNA). Through this mechanism of action, there is a reduction or suppression of transcription of genes that encode cytokines but do not shown GRE in promoting regions.

In addition to the effects described above, known as genomic mechanisms, glucocorticoids also exert non-genomic effects, characterized by present a rapid onset of action (<15 minutes) and do not depending on transcription gene or protein translation. Among the non-genomic effects is the direct interaction of lipophilic steroids with cell membranes, modifying their properties physicochemical and affecting the activity of proteins associated with membranes; the stabilization of the lysosomal membrane is an example of this effect.

The actions described for hydrocortisone sodium succinate are those expected for glucocorticoids: anti-inflammatory and immunosuppressive, with some activity mineralocorticoid:

- reduction of inflammation by stabilizing leukocyte lysosomal membranes, preventing the release of destructive enzymes or reducing leukocyte adhesion to the capillary endothelium;
- inhibition of macrophage accumulation in inflamed areas;
- reduction of the permeability of the capillary wall and consequent reduction of edema;
- antagonization of histamine activity and kinin release;
- reduction of fibroblast proliferation, collagen deposition and subsequent decreased formation of scar tissue;
- stimulus for bone marrow erythroid cells, production of neutrophilia and eosinopenia and prolongation of red cell and platelet survival time;
- promotion of gluconeogenesis, redistribution of peripheral fat to the central region and protein catabolism;
- reduced intestinal calcium absorption and increased renal calcium excretion;
- suppression of the immune response by reducing the activity and volume of the lymphatic system and producing lymphocytopenia;
- decreased immunoglobulin and complement concentrations and the passage of immune complexes across the basement membrane;
- depression of tissue reactivity to antigen-antibody interaction;
- in pharmacological doses, suppresses the release of adrenocorticotropic hormone by pituitary gland, with consequent suppression of secretion of endogenous glucocorticoids (secondary adrenal insufficiency). The degree of suppression of the hypothalamus-pituitary adrenal depends on the dose, frequency and duration of therapy.

Pharmacokinetic properties

Absorption

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory effects of hydrocortisone. When administered parenterally in amounts equimolar, the two compounds have equivalent biological activity. Sodium succinate hydrocortisone is highly water-soluble, allowing intravenous administration of high doses of hydrocortisone in a small volume of diluent, which is particularly useful in situations where high plasma concentrations of hydrocortisone should be achieved quickly.

After intravenous injection of hydrocortisone sodium succinate, the effects are already evident in approximately 1 hour, and excretion is almost complete in 12 hours, so that if constant serum concentrations are necessary, injections should be administered every 4 to 6 hours. Hydrocortisone sodium succinate also rapidly absorbed after intramuscular administration and presents a pattern of excretion similar to that seen after intravenous injection.

Distribution

The half-life of hydrocortisone sodium succinate after intravenous administration is 1.5 to 3.5 hours and the duration of its anti-inflammatory effects is close to the duration of suppression of the hypothalamic-pituitary-adrenal axis, which varies from 1.25 to 1.5 days for a 250mg dose.

Like most glucocorticoids, hydrocortisone sodium succinate is rapidly removed from circulation and distributed to the muscles, liver, skin, intestines and kidneys; in addition, it crosses the placental barrier and appears in breast milk.

As well as the cortisol, hydrocortisone sodium succinate binds to glucose-binding globulin corticosteroids and albumin.

Metabolism and elimination

Hydrocortisone sodium succinate is metabolized in most tissues, mainly in the liver, to inactive compounds, which are excreted by the kidneys, primarily as glucuronides and sulphates, but also as products not conjugates. Small amounts of the non-metabolized drug are also excreted in the urine.

4. CONTRAINDICATIONS

Androcortil® should not be used by patients with hypersensitivity to components of the formula.

Androcortil® is contraindicated in cases of systemic fungal infections.

Long-term treatments with corticosteroids should be avoided.

5. WARNINGS AND PRECAUTIONS

General

In patients undergoing corticosteroids, subjected to unusual stress, higher dose of fast acting corticosteroids before, during and after stressful situation. Secondary adrenocortical insufficiency of drug origin may be reduced to a minimum by gradual dose reduction. Such type of insufficiency the relative pressure can persist for months after treatment ceases, therefore, in any stressful situation that occurs during this period, therapy should be reinstituted hormonal. If the patient is already receiving steroids, it may be necessary to increase the dosage. Since mineralocorticoid secretion may be impaired, salt and / or mineralocorticoids are administered simultaneously.

Corticosteroids can cause drop in resistance and inability of infection if circumscribe. In addition, corticosteroids can produce subcapsular cataracts glaucoma with possible damage to the optic nerves and can stimulate the establishment of secondary eye infections due to fungi and viruses.

While on corticosteroids, patients should not be vaccinated against smallpox. Other methods of immunization should not be used in patients who received corticosteroids, especially in high doses, due to the possible risks of neurological complications and lack of antibody response. However, they can be immunizations are performed in patients receiving corticosteroids as replacement.

Psychological and / or physiological dependencies can arise with the long-term use of corticosteroids. The withdrawal symptoms that may occur include fever, anorexia, vague pains, weakness and lethargy. In patients with hyperthyroidism and in with cirrhosis, there is an accentuation of the effect of corticosteroids.

Psychological disorders may appear when using corticosteroids, ranging from euphoria, insomnia, mood swings, personality changes and severe depression even weak overt manifestations of psychosis. Also, emotional instability or pre-existing psychotic tendencies can be exacerbated by corticosteroids. The use of hydrocortisone sodium succinate in active tuberculosis should be restricted to cases of tuberculous meningitis with imminent block, in which a corticoid is used in combination with an appropriate anti-tuberculosis regimen. If corticosteroids are indicated for patients with latent tuberculosis or reactivity to tuberculin, it is necessary careful surveillance, as reactivation of the disease may occur. During therapy prolonged with corticosteroids, these patients should receive chemoprophylaxis. For prevention of anaphylactic reactions (e.g., bronchospasm) in patients under parenteral corticosteroid therapy, appropriate measures should be taken to precaution before administration, especially when the patient presents history of allergy to any drug. In some patients, steroids can increase or decrease motility and sperm count.

Corticosteroids should be used with caution in patients with ocular herpes simplex, due to the possibility of cornea perforation, the same caution must be taken for non-specific ulcerative colitis, if there is a likelihood of imminent perforation, abscess or other pyogenic infection, in diverticulitis, recent intestinal anastomosis, hypertension, osteoporosis and myasthenia gravis.

Carcinogenesis, mutagenesis, impaired fertility

There is no evidence that corticosteroids are carcinogenic, mutagenic or impair fertility.

Pregnancy

Some animal studies show that corticosteroids, when administered in high doses, can cause fetal malformations. No studies have been conducted in human reproduction. Therefore, the use of this medication during pregnancy, in nursing mothers or potentially fertile women may only occur if the potential benefit justifies the potential risk to the fetus. The corticosteroids cross the placenta quickly. Newborns patients who have received substantial doses of corticosteroids during pregnancy should be carefully observed and evaluated for signs of adrenal insufficiency.

Risk category: C

This medicine should not be used by pregnant women without guidance doctor or dental surgeon.

Lactation

The use of corticosteroids during breastfeeding is not recommended, since hydrocortisone sodium succinate is excreted in human milk, causing inhibition of the production of endogenous steroids and growth suppression in children.

Pediatric use

Prolonged use of hydrocortisone sodium succinate can cause growth in children and adolescents; thus, growth and development should be monitored with prolonged therapy and the dose should be titrated to the lowest effective dose. Long-term therapy can also induce osteoporosis and fractures and may lead to inhibition of bone growth reached by inhibiting bone formation. Therefore, bone mass should be periodically assessed by bone densitometry and must ensure an adequate intake of calcium and vitamin D (by diet or supplementation).

Use in elderly patients

These patients may be more likely to develop hypertension and women, after menopause, may also be likely development of corticosteroid-induced osteoporosis.

Prolonged hydrocortisone sodium succinate therapy may cause mass loss muscle and muscle weakness, healing difficulties, skin atrophy, osteoporosis with vertebral fractures and compression, aseptic necrosis of the femoral head or fracture of long bones. Before starting glucocorticoid therapy in post menopause women, you should keep in mind that these women are especially susceptible to osteoporosis.

Patients with liver failure

Patients with cirrhosis may have an exaggerated response to glucocorticoids.

Patients with renal failure

Glucocorticoids should be used with caution in this patient population.

Other clinical conditions

Patients with low serum albumin concentrations may be more susceptible to glucocorticoid effects than those with normal albumin concentrations. The metabolic clearance of hydrocortisone sodium succinate may be decreased in patients with hypothyroidism and increased in those patients with hyperthyroidism.

This medication can cause doping.

6. DRUG INTERACTIONS

- phenobarbital, phenytoin, rifampicin and ephedrine: may increase the clearance of corticosteroids, reducing their therapeutic effects and may require an adjustment in corticosteroid measurement.

- troleandomycin and ketoconazole: they can inhibit the metabolism of corticosteroids, causing a decrease in its clearance. Consequently, the dose of corticosteroids should be titrated to avoid toxicity.

- acetylsalicylic acid and salicylates: corticosteroids can increase the clearance of acetylsalicylic acid, therefore acetylsalicylic acid should be used with caution in association with corticosteroids in cases of hypoprothrombinemia.

Salicylates can have their serum concentrations decreased or increase the risk of toxicity during the concomitant use with corticosteroids.

- Coumarinic anticoagulants: corticosteroids alter the response of the anticoagulants; therefore coagulation indices should be monitored in order to keep the anticoagulant effect adequate.

- amphotericin B and carbonic anhydrase inhibitors: concomitant use with corticosteroids may result in hypokalemia, as serum potassium concentrations and cardiac function should be monitored during this association. Can also an increase in calcium depletion occurs with risk of osteoporosis hypocalcaemia.

- Oral contraceptives and estrogens: they can alter the metabolism and the connection to proteins, decrease clearance and increase elimination half-life and effects therapeutic and toxic effects of corticosteroids, so the corticosteroid dose should be adjusted during this association.

- Potassium-depleting diuretics: may cause the appearance of hypokalemia, in that case, the patient must be observed by the doctor.

- Digitalis glycosides: may increase the possibility of arrhythmias or intoxication digitalis associated with hypokalemia.

- Non-hormonal anti-inflammatory drugs and alcohol: may increase the incidence or severity gastrointestinal ulceration or bleeding.

- Oral antidiabetics and insulin: can increase the concentration of blood glucose, therefore, if necessary, readjust the dosage of the hypoglycemic agent.

- Immunosuppressants: may increase the risk of infections and development of lymphomas.

- Depolarizing neuromuscular blockers: may increase the risk of respiratory depression, for prolonged relaxation.

- Live virus vaccines or other immunizations: may increase the risk of reactions adverse.

Interference in laboratory tests

- Nitroblue tetrazolium test for bacterial infection: false result may occur negative, compromising the test result; suppression of skin test reactions, including tuberculin and histoplasmin, allergic tests.

7. DRUG STORAGE CARE

BEFORE PREPARATION, STORE IN ROOM TEMPERATURE (15ºC to 30ºC). PROTECT FROM LIGHT AND MOISTURE.

The obtained solution must be used immediately after preparation. After use, discard any unused solution.

Expiration date: 18 months from the date of manufacture.

Batch number, manufacturing and expiration dates: see packaging.

Attention: The batch number and expire date printed on vial may become unreadable or even lost if the packaging comes into contact with any type of alcoholic solution.

Do not use medicine expired. Keep it in your original packaging.

Physical and organoleptic characteristics: White or almost white powder, odorless, hygroscopic. After reconstitution, limpid transparent solution.

Before using, observe the appearance of the medicine.

All medication should be kept out of the reach of children.

8. DOSAGE AND HOW TO USE

Adults

The recommended dose is 100mg to 500mg, intramuscularly or intravenously (preferably), which can be repeated at intervals of 2, 4 or 6 hours, depending on clinical condition and patient response.

The initial intravenous dose should be administered over a period of 30 seconds (dose of 100mg) and 10 minutes (doses of 500mg or higher).

The maintenance dose, if necessary, should not be less than 25mg per day.

Kids

Adrenocortical insufficiency: the recommended dose is 186 to 280mcg (0.186 to 0.28mg) per kg of body weight or 10 to 12 mg per square meter of body surface per day, in divided doses, intramuscularly or intravenously (preferably).

Other indications: the recommended dose is 666mcg (0.666mg) to 4mg per kg of weight or 20 to 120mg per square meter of body surface every 12 or 24 hours, intramuscularly.

Reconstitution guidelines

- Shake the vial, still closed, to loosen the powder from the bottom, with light taps;
-Remove the seal from the vial and disinfect the rubber cap with cotton and 70% alcohol;
- Perform the disinfection of the neck of the diluent ampoule with cotton and 70% alcohol, open the ampoule, aspirate the contents and inject the diluent in a swirl into the vial to provide a more effective homogenization;
-Pull out the contents and remove any bubbles from the syringe, expelling the air and only the solution;
- Change the needle;

Preparation of the solution

Androcortil® 100mg: For intravenous or intramuscular injection, reconstitute the solution adding, with asepsis, 2mL of diluent (water for injections) to the contents of the vial-ampoule. Final volume 2mL.

Shake well to ensure complete dissolution. The solution thus obtained must be used immediately after preparation. After use, discard any unused solution.

The solution can be administered by infusion using 500 or 1,000mL of serum glycosylated at 5%, saline or glycophysiological solution (if the patient is not under sodium restriction).

9. ADVERSE REACTIONS

Liquid and electrolyte disorders: sodium retention, fluid retention, insufficiency cardiac arrest in susceptible patients, loss of potassium, hypocalcemic alkalosis and hypertension.

Musculoskeletal: muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of the femur heads and humerus, pathological fracture of long bones and rupture of tendons.

Gastrointestinal: peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine, particularly in patients with intestinal disease, pancreatitis, abdominal distension and ulcerative esophagia.

Dermatological: impaired wound healing, thin and fragile skin, petechiae and ecchymosis, erythema, hypersudoresis, possible suppression of reactions to skin tests, other skin reactions, such as allergic dermatitis, urticaria and angioneurotic edema.

Neurological: seizures, increased intracranial pressure with papilledema (cerebral pseudotumor), usually after treatment, vertigo and headache.

Endocrine: menstrual irregularities, development of cushingoid status, suppression of the adrenal pituitary axis, manifestations of diabetes mellitus (latent).

Ophthalmic: posterior subcapsular cataract, increased eye pressure, exophthalmos.

Immune system: masking infections, activating latent infections, opportunistic infections and suppression of the reaction to skin tests.

Symptoms of anaphylactic reactions such as bronchospasm, laryngeal edema may appear and hives.

10. OVERDOSE

Overdose treatment is symptomatic. In the event of accidental ingestion or administration of doses well above those recommended, it is recommended to adopt the measures usual controls for vital functions.

In case of poisoning call 0800 722 6001, if you need further guidance.

LEGAL SAYINGS
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SALE UNDER MEDICAL PRESCRIPTION

This package insert has been updated in accordance with Standard Label approved by Anvisa on 10/24/2016.