

Corticosteroid therapy in inflammatory bowel diseases



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Corticosteroid therapy in inflammatory bowel diseases

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The discovery of **cortisol** by E. Kendall and O. Wintersteiner in 1937, and its synthesis by T. Reichstein in 1938, made it possible for P.S. Hench to use this substance for the first time in 1948 to treat a patient with rheumatoid arthritis.

Cortisol belongs to a class of hormones known as **corticosteroids** (often simply called “cortisone” in everyday speech).

Hormones – this word comes from Greek and means “to set in motion” – are the body’s own messengers. They are usually released from special glands in response to a stimulus and are then carried in the blood to their destinations in the body. Hormones then control a number of metabolic processes in their target organs.

The rapid and potent anti-inflammatory effect of cortisol quickly established corticosteroids as an effective treatment in cases of acute and chronic inflammation, and also helped its three discoverers win the Nobel Prize in 1950.

Even in the early days, it was clear that the desired effects of the corticosteroids were accompanied by unwanted side effects. Only gradually were ways found to avoid these effects as far as possible: by using the drugs in a targeted manner, and by limiting their use.

Introduction

Treatment with corticosteroids was also a significant step forward for patients with **inflammatory bowel disease**. Even as late as the 50s, the life-expectancy of these patients was significantly reduced because acute flare-ups could only be treated to a very limited extent. For this reason, many young patients died of their disease. The introduction of corticosteroids has almost restored the life-expectancy of patients with Crohn's disease and ulcerative colitis to normal values. The challenge today is to use corticosteroids in such a way that patients also enjoy the highest possible quality of life as a result of their use.

"Cortisone phobia" is a widespread problem, which stems from inadequate knowledge among the general public and also among some patients with inflammatory bowel disease. This patient advice leaflet aims to combat this lack of knowledge by explaining the most important aspects of treatment with corticosteroids in a comprehensible manner.

The natural role and regulation of corticosteroids in the body

The endogenous (naturally occurring in the body) hormone cortisol and its precursor cortisone are produced in the **adrenal cortex**.

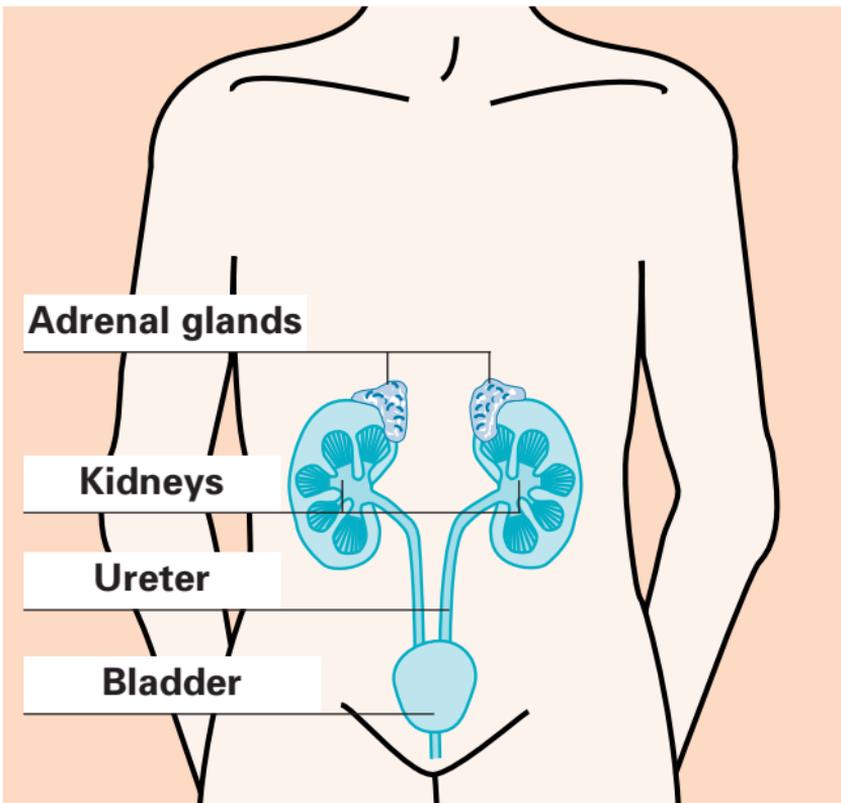


Fig. 1: **Location of the adrenal glands in relation to the kidneys**

The adrenal glands, consisting of the medulla and the adrenal cortex, are among the organs in the body that act as glands (Fig. 1).

Corticosteroids in the body

Cortisol is essential for the body. The production of cortisol in the adrenal glands is stimulated by a controlling hormone, the **adrenocorticotrophic hormone (ACTH)** (Fig. 2).

ACTH is produced in the pituitary gland (hypophysis), a gland that is only the size of a cherry stone and which weighs less than 1 g.

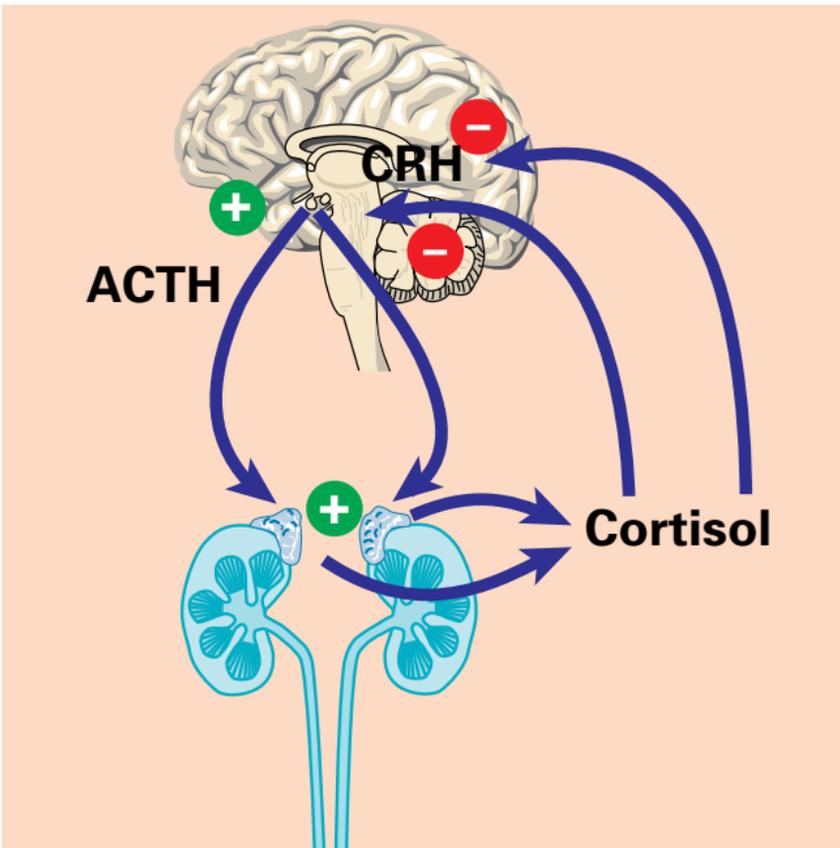


Fig. 2: **The cortisol control system in the hypothalamus, hypophysis and adrenal cortex**

The release of ACTH is controlled by a further hormone, the so-called **corticotrophin releasing hormone (CRH)**.

CRH is produced in the mid-brain in the central nervous system (hypothalamus).

Within this complex system, cortisol regulates its own release: High concentrations of cortisol inhibit the release of cortisol.

This type of control is known as a self-regulating feedback mechanism. Nervous and inflammatory stress factors also have an effect on this regulatory loop.

Cortisol is normally produced in a **rhythm that depends upon the time of day**. The largest amounts are released in the early morning, and smaller amounts are released later on (Fig. 3). A second, smaller peak does not occur until the evening. Altogether, the adrenal cortices produce about 8–25 mg cortisol per day.

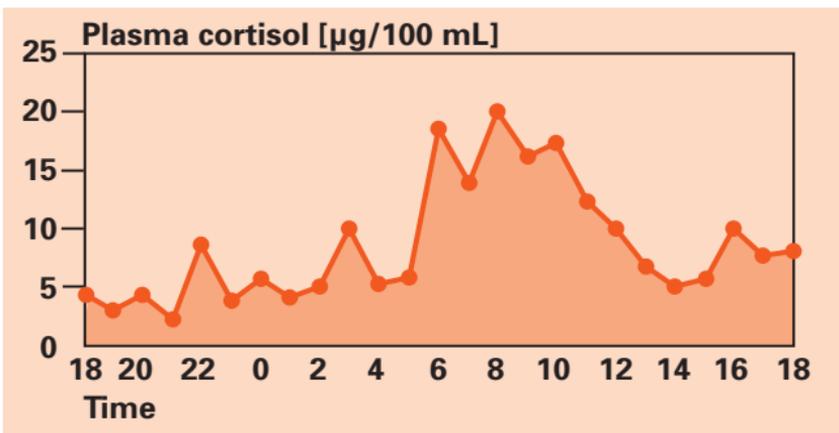


Fig. 3: **Diurnal (related to the time of day) rhythm of blood cortisol levels**

Corticosteroids in the body

When under severe stress, such as a serious illness, the body requires more cortisol. This is why the adrenal cortices have the ability to produce up to 200–300 mg per day in such situations.

All corticosteroids, including cortisol, act by “binding” to specific **receptors** (recognition sites) on cells and then altering their metabolism. This is how they stimulate the breakdown of proteins, for instance. Since almost all cells in the human body have this type of receptor, corticosteroids act upon almost all cells.

These varied effects can be broadly divided into three groups:

1. the **anti-inflammatory effects**, which are also important for efficacy in the treatment of inflammatory bowel disease,
2. the **metabolic effects (effects on general metabolism)**, which are also responsible for the occurrence of side effects and
3. the effects on **fluid balance (mineral metabolism)**.

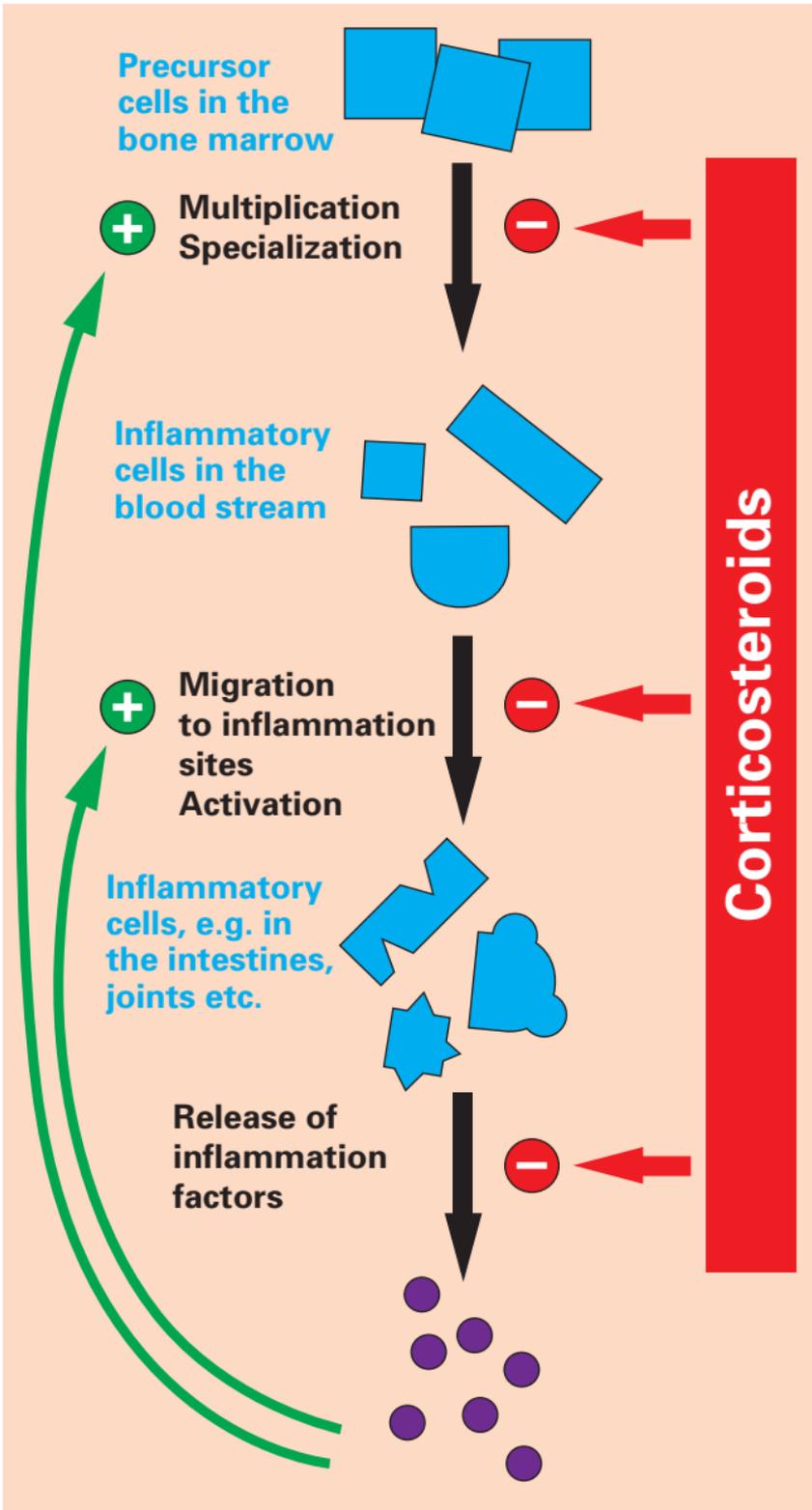


Fig. 4: **Inhibition of inflammation by corticosteroids**

Anti-inflammatory effects of corticosteroids

The **anti-inflammatory effect** is due to the fact that corticosteroids inhibit the multiplication (proliferation) and development (differentiation) of inflammatory cells in the bone marrow, the migration of inflammatory cells from the blood into the intestines, and the activation of these inflammatory cells (Fig. 4). Corticosteroids also have a direct effect upon all types of inflammatory cells, as well as on white blood cells (leukocytes). In these cells, corticosteroids inhibit the release of inflammatory hormones, such as cytokines, which stimulate inflammation.

The effects of corticosteroids on metabolism

The effects on general metabolism are even more varied. Corticosteroids affect metabolism in the liver, the muscles, the fatty tissues, the bones and ligaments, and many other organs.

The effect of corticosteroids on fluid balance

The effect on fluid balance is due to the fact that cortisol bears a certain resemblance to another hormone – aldosterone – which affects fluid balance by regulating the excretion of minerals in the kidneys. Like aldosterone, cortisol increases the retention of water in the body.

Treatment with corticosteroids

Not long after cortisol was first used in the treatment of inflammatory diseases, attempts were made to increase its efficacy, and at the same time reduce unwanted side effects through chemical modifications.

The use of synthetic corticosteroids to improve efficacy and tolerability

The development of corticosteroids such as prednisone, prednisolone and 6-methylprednisolone resulted in corticosteroids with very little or no effects on mineral metabolism, while at the same time increasing their efficacy as anti-inflammatories.

Prednisolone and prednisone have an anti-inflammatory effect about four times as great as that of endogenous cortisol, and 6-methylprednisolone is even five times more effective.

Since all anti-inflammatory and metabolic effects are mediated by the same receptors on the cells, it is very difficult to separate the desired effects from the unwanted side effects. In order to achieve progress here, attempts have been made to transport the active substance directly to the site of inflammation in order to minimize the systemic effects and the effects produced by circulation in the blood – and thus also the effects on the entire body.

Different pharmaceutical forms for the treatment of ulcerative colitis

Initially, pharmaceutical forms for the treatment of ulcerative colitis were produced that resulted in a high concentration of corticosteroid in particular bowel segments only, namely in those parts where the inflammation is located. The development of **enemas** made it possible to achieve this goal in part. The use of corticosteroid enemas can achieve relatively high local concentrations of corticosteroid in the rectum and distal sections of the large intestine (Fig. 5).

Nevertheless, some of the corticosteroid applied in this way is absorbed through the intestinal mucosa (the lining of the intestines) causing unwanted side effects, albeit to a reduced extent. Corticosteroid **foams** are just as effective as enemas, but they are preferred over enemas by most patients because they are easier to use. In addition, because of its consistency and volume, most patients find foam easier to keep in. In more severe cases of the disease, however, corticosteroids must be administered in the form of tablets, capsules, or even as intravenous injections, in order to achieve an adequate effect.

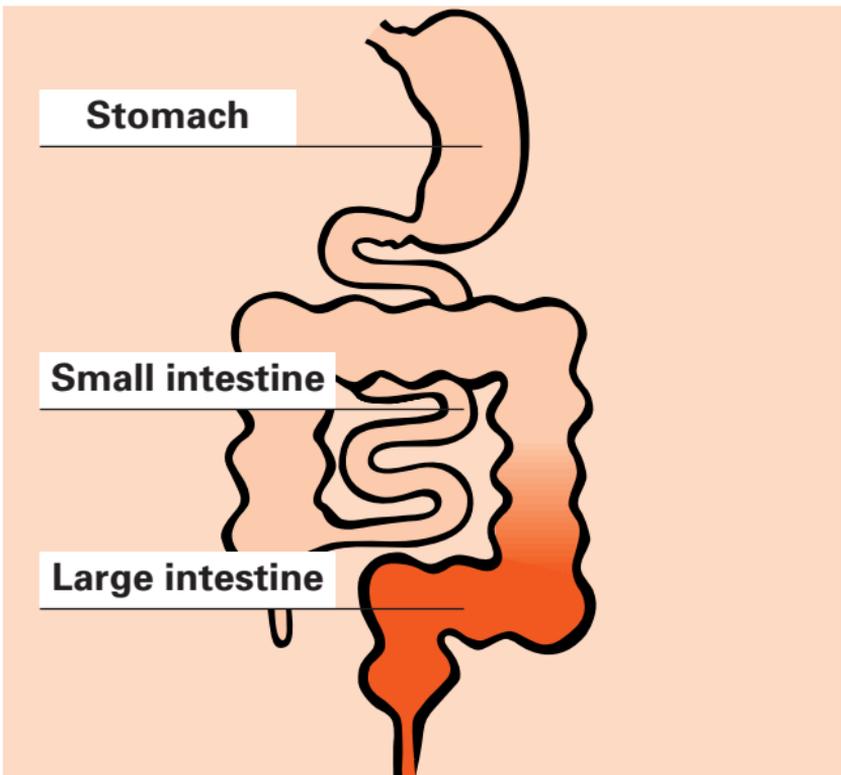


Fig. 5: **Location of efficacy of corticosteroid enemas and foam preparations in the large intestine**

Topical corticosteroids

In an effort to preserve the efficacy of corticosteroids while further reducing the side effects of these substances, so-called **topical corticosteroids** have been developed in recent years. The term “topical” means that the effect is predominantly local, i.e. active at the site of inflammation. The principle of topical corticosteroids will now be explained using the example of budesonide, which has long been used successfully in treating asthma and acute flare-

In order for oral budesonide to arrive at the local sites of inflammation in the intestines, it is crucial that it is not absorbed into the blood stream in the upper segments of the small intestine. Therefore, a special coating must be used to ensure that the active substance is only released at the sites of inflammation (in the case of Crohn's disease, this means the transition area between the small and large intestine in particular, and in the case of ulcerative colitis, the large intestine in particular).

However, it should be noted that these coatings mean that inflammation in the esophagus, the stomach, and the upper parts of the small intestine, such as the duodenum, cannot be treated in this way. Furthermore, in cases of severe disease, it may be necessary to use systemically active corticosteroids.

Efficacy in inflammatory bowel disease

Generally speaking, corticosteroids are currently the most effective drugs for the treatment of acute flare-ups of inflammatory bowel disease (ulcerative colitis and Crohn's disease). Long-term treatment with systemically active corticosteroids should, however, be avoided where possible.

Ulcerative colitis

Mild to moderately active ulcerative colitis

Treatment with 5-aminosalicylic acid (mesalazine) is adequate for most cases of mild to moderately active ulcerative colitis. The next line treatment to consider is a combination mesalazine therapy consisting of tablets or granules and enemas/foam preparations. As another option is the administration of 9 mg of oral budesonide-MMX.

Where appropriate, a short course of systemic corticosteroids (for example 40 mg per day of prednisolone), with a rapid dosage reduction of 10 mg every 5 days and a halt to corticosteroid treatment within 3 weeks, may lead to a more rapid alleviation of the symptoms. Most patients respond rapidly to this treatment. However, the occurrence of side effects often somewhat diminishes the therapeutic advantages of systemic corticosteroid therapy.

Left-sided ulcerative colitis

In left-sided ulcerative colitis, in which only the final 50 cm of the large intestine is affected, 5-aminosalicylic acid (mesalazine) enemas or foam preparations are preferred, and – where necessary – corticosteroid foam preparations or enemas, because these achieve the highest concentrations of active sub-

stance in the inflamed area. In severe cases, it may be necessary to administer a combination of 5-aminosalicylic acid (mesalazine) and corticosteroid rectally, or possibly even a combination mesalazine therapy composed of enemas and oral forms (tablets, granules).

Highly active ulcerative colitis

Highly active ulcerative colitis always represents an acute danger to the patient. In these cases, it is often unclear whether tablets or granules can still be effective. On the other hand, enemas and foam preparations generally cannot be retained for a sufficient period of time owing to the severe diarrhea. This is why inpatient treatment and the intravenous administration of high doses of corticosteroids are necessary in such cases. Depending on the severity of the disease, additional therapeutic measures may be required.

Inactive ulcerative colitis – maintenance of remission

Based on what we currently know about corticosteroids, they should not be used for maintenance of remission (remission = freedom from symptoms/absence of active disease), because they are not effective in this regard, and the possible side effects may be a burden on the patients. The first-line (i.e. preferred)

Treatment with corticosteroids

agents in such cases are preparations containing 5-aminosalicylic acid (mesalazine). This treatment has been proven to reduce the risk of colorectal cancer.

In patients who do not tolerate mesalazine, *E. coli Nissle 1917* may be used.

Pouchitis

When complete surgical removal of the colon is required in patients with ulcerative colitis, a small bowel reservoir (pouch) can enable regular bowel movements in many cases.

However, in some cases, this pouch may become chronically inflamed. The standard treatment for this involves the administration of the antibiotic metronidazole. Alternatively, budesonide can be used as an enema or foam if this is better tolerated.

Crohn's disease

Mild to moderately active Crohn's disease

Today, mild to moderate flare-ups of acute Crohn's disease are treated with either 5-aminosalicylic acid (mesalazine) or corticosteroids. Here, corticosteroids are more effective than 5-aminosalicylic

Treatment with corticosteroids

acid preparations. The same applies to the predominantly topically active corticosteroid budesonide. In the case of corticosteroids, the 6-month treatment regimen (Tab. 1) for the treatment of acute Crohn's disease is increasingly being abandoned because the majority of patients respond much more quickly to this kind of treatment. Moreover, the rate of side effects for systemically active corticosteroids is relatively high.

Nowadays, depending on disease activity, a variable dose reduction is recommended.

The topical corticosteroid budesonide is used as an oral preparation in the treatment of ileocaecal Crohn's disease. It is taken in the form of a capsule con-

Week of treatment	Daily dose of prednisolone
1	60 mg
2	40 mg
3	35 mg
4	30 mg
5	20 mg
6	15 mg
7–14	10 mg
3–6 months	5–10 mg

Tab. 1: **Treatment regimen for acute Crohn's disease using prednisolone as an example**

Treatment with corticosteroids

taining granules that are resistant to gastric acid.

The granules are also available in a sachet containing the daily dose as a single portion. Budesonide is then released from the granules inside the small intestine and the large intestine, and acts directly on the intestinal mucosa. After that, it is rendered inactive in the liver. Due to this mechanism of action, it is particularly effective in treating cases where the final portion of the small intestine (the terminal ileum) or the first part of the colon (caecum) is affected. If the rectum is also affected, additional treatment with enemas or foam preparations will be necessary, or systemically active corticosteroids will need to be used.

Highly active Crohn's disease

As with ulcerative colitis, such cases are also serious and require inpatient treatment and the administration of a high dose of corticosteroids in the form of injections. If necessary, additional therapeutic measures must also be taken.

Inactive Crohn's disease – maintenance of remission (remission = period of absence of symptoms)

Corticosteroids should not be used for maintenance of remission.

Microscopic colitis (collagenous colitis and lymphocytic colitis)

Because cases of microscopic colitis are rare and can only be diagnosed by careful examination of tissue samples from the colon (normally, they cannot be detected macroscopically in a colonoscopy), it often takes time before the diagnosis is made. The condition causes chronic watery diarrhea.

Budesonide in the form of capsules or granules is the first-line treatment for both forms of microscopic colitis, collagenous colitis and lymphocytic colitis, as it is very effective and has few side effects.

The standard dose is 1 x 9 mg a day or 3 x 3 mg a day. With this treatment, both stool consistency and the frequency of bowel movements improves in about 90% of patients and, in about 80% of patients with collagenous colitis, there is improvement in the collagen deposits that form in the wall of the colon. This is even true in cases in which other therapies, such as 5-aminosalicylic acid, metronidazole, or prednisolone have

Treatment with corticosteroids

failed. The budesonide dose can be reduced during the course of treatment in accordance with the symptoms. However, many patients still require long-term treatment.

Endemic sprue / celiac disease

Endemic sprue or celiac disease is a chronic inflammatory disorder of the small intestine, which is triggered by gluten and gliadin, which are proteins found in grains. Patients experience diarrhea, iron and vitamin deficiencies, weight loss, and growths in the small intestine.

The standard treatment is a diet that is free of gluten and gliadin.

Thankfully, cases of endemic sprue or celiac disease that do not respond to this treatment are rare. When such treatment-refractory cases occur, patients are treated with prednisolone and, more recently, with budesonide, a corticosteroid that is associated with a much lower rate of side effects.

Tolerability and side effects

Prolonged treatment with systemically active corticosteroids leads to side effects that often necessitate a dose reduction or discontinuation of treatment. The simultaneous appearance of

Possible side effects of corticosteroids

- Weight gain with abdominal obesity, moon face, buffalo hump
- Striae (stretch marks on the skin), ecchymoses (small hemorrhages in the skin), acne
- Atrophy (shrinkage) of the adrenal cortices
- Increase in blood glucose and cholesterol levels
- Increase in blood pressure
- Osteoporosis (bone loss) and disorders of blood flow in the bones (bone necrosis)
- Electrolyte imbalance, e.g. lack of potassium
- Cataract and glaucoma
- Insomnia, psychosis
- Nerve damage
- Inflammation of the muscles, muscle wasting
- Increased susceptibility to infection (tuberculosis, fungal diseases)
- Growth disorders (in children)

Tab. 2: **Possible side effects of corticosteroids**

a number of visible side effects of corticosteroids, such as weight gain with abdominal obesity, moon face, buffalo hump, and stretch marks on the skin (striae), is also known as **Cushing's syndrome**. The possible side effects of corticosteroids are listed in Table 2.

The long list of possible problems associated with corticosteroid treatment also

Treatment with corticosteroids

highlights the importance of the search for new corticosteroids with fewer side effects.

In the following section, some of the possible side effects of corticosteroids will be described in greater detail, together with advice as to what can be done to combat them.

Osteoporosis is a common and potentially severe complication of prolonged treatment with corticosteroids. Spontaneous fractures may occur. Corticosteroids inhibit bone formation and stimulate the breakdown of bone by inhibiting the uptake of calcium in the intestines and stimulating the release of parathyroid hormone (a hormone that promotes the breakdown of bone). Calcium and vitamin D supplements must be taken in the case of deficiency. There are indications that budesonide is much better tolerated than systemic corticosteroids, including with regard to the risk of osteoporosis.

Corticosteroid-induced bone necrosis is a severe disorder of the blood supply to the bone.

Fortunately, it is rare. It predominantly affects the hip joint and manifests itself as pain.

Treatment with corticosteroids

Prolonged treatment with corticosteroids may lead to atrophy (shrinkage) of the adrenal glands because the body's natural cortisol production is suppressed.

It is therefore essential to avoid stopping treatment with systemic corticosteroids abruptly. They must instead be tapered down very gradually by reducing the dose so that the adrenal cortex has sufficient time to regenerate and begin secreting cortisol again. Severe fatigue and feeling weak are typical symptoms that may occur if corticosteroids are phased out too quickly.

Other (rare) side effects include clouding of the lens of the eye (cataracts), and an increase in the internal pressure of the eye (glaucoma). In order that a diagnosis can be made at an early stage, regular ophthalmological examinations should be performed in patients undergoing long-term treatment with corticosteroids.

In some cases, it will be necessary to change the preparation being used or to discontinue the treatment.

The suppression of the immune system caused by corticosteroids also weakens resistance to infection. Therefore, if there are palpable masses in the abdomen, the presence of an abscess (collection of pus) must be ruled out before beginning treatment with corticosteroids.

Treatment with corticosteroids

Pregnancy and cortisone therapy

There is no increased risk of miscarriage. If high doses of corticosteroids are used during the final phase of pregnancy, the newborn will need to be carefully examined by a pediatrician. Insufficient treatment of inflammatory bowel disease is more dangerous for both the mother and the baby than cortisone treatment with the appropriate dose.

There is not yet enough data available to make a general recommendation regarding the administration of budesonide during pregnancy.

Breastfeeding and cortisone therapy

Because cortisone may be excreted in breast milk, thus entering the infant's body, suppression of cortisone production in the infant is a possibility. This should therefore be carefully monitored by a pediatrician. Permanent damage is not expected.

Glossary

5-aminosalicylic acid (5-ASA; mesalazine): an active ingredient in many medicines for the treatment of inflammatory bowel disease.

Abscess: a collection of pus.

ACTH: adrenocorticotropic hormone; a controlling hormone that stimulates the formation and secretion of corticosteroids. ACTH is produced in the pituitary gland.

Aldosterone: a hormone of the adrenal cortex that affects fluid balance.

Bone necrosis: a severe disorder of the blood supply to the bone, associated with destruction of bone tissue.

Budesonide: a locally (topically) acting, potent corticosteroid, which can be administered in the form of capsules, granules, tablets, foams or enemas.

Cataract: clouding of the lens of the eye caused by a variety of factors (congenital or acquired).

Colon: large intestine.

Collagenous colitis: a type of microscopic colitis characterized by the development of a band of collagen fibers over 10 μm in thickness.

Corticosteroids: a class of hormones that are released from the adrenal cortices, e.g. cortisol.

Cortisol: a hormone belonging to the corticosteroid family; regulates many metabolic processes.

CRH: corticotropin releasing hormone, a controlling hormone that regulates the secretion of ACTH. CRH is produced in the hypothalamus.

Crohn's disease: an inflammatory disease of the digestive tract, named after Dr. Burrill B. Crohn, the doctor who first described the disease. Common in the region of the lower ileum (part of the small intestine) and the ascending colon.

Cushing's syndrome: a typical condition that is triggered by elevated levels of cortisol in the plasma and which can occur if corticosteroids are administered for a prolonged period of time or at high doses.

Cytokines: hormones that mediate inflammatory reactions (inflammation mediators).

Differentiation: further development (specialization) of cells.

Endemic sprue / celiac disease:

a chronic inflammatory disorder of the small intestine triggered by intolerance of grain proteins.

Glaucoma: general term for diseases of the eye in which the internal pressure of the eye is elevated.

Hormone: a messenger substance produced in the body that regulates metabolic processes.

Hypothalamus: the central nervous region of the interbrain.

Ileum: the lowest section of the small intestine.

Immune system: a complex system that defends the body against foreign substances.

Lymphocytic colitis: a type of microscopic colitis characterized by increased numbers of lymphocytes in the tissue samples.

Microscopic colitis: a chronic inflammatory disorder of the colon, which can only be diagnosed by examination of tissue samples obtained from the colon using a microscope (see also collagenous colitis and lymphocytic colitis).

Migration: movement of inflammatory cells from the blood into the intestines.

MMX: Multi Matrix coating; a coating that allows targeted release of the active substance in the large intestine

Osteoporosis: loss of bone tissue due to increased bone loss and/or reduced formation of bone.

Parathyroid hormone: a hormone that is produced in the adrenal glands whose effects include increasing the rate of bone remodeling.

Pouchitis: inflammation of the pouch after removal of the colon in the case of ulcerative colitis.

Proliferation: multiplication of cells.

Psychosis: impairment of the state of mind causing a fundamentally altered experience of reality.

Remission: a state characterized by the absence of symptoms in the presence of chronic disease.

Ulcerative colitis: chronic inflammation of the large intestine.

Further information for patients with inflammatory bowel diseases:

- Rectal treatment for inflammatory bowel disease (S97e)
29 pages
- Microscopic colitis – Collagenous and lymphocytic colitis (Bu82e)
27 pages
- Ulcerative colitis and Crohn's disease
An overview of the diseases and their treatment (S80e)
63 pages
- Diet and Nutrition in Crohn's Disease and Ulcerative Colitis
Important Questions – Real Answers (S84e)
62 pages
- Crohn's disease and its associated disorders (S85e)
44 pages

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