THE HISTORY OF GLUCOCORTICOIDS AND ITS INTRODUCTION TO DENTISTRY

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Preface

This project thesis is submitted as partial fulfilment of the requirements for the degree Master of Odontology at the Faculty of Dentistry, University of Oslo, graduating January 2014.

The reason being our choice of subject for the project thesis is our impression that glucocorticoids have a limited use in dental practice in Norway. During our lectures in pharmacology and oral surgery, however, we understood that this was a family of drugs with many advantageous properties which could be very useful during our profession as dentists.

Hence, we wanted look at glucocorticoids in a historical perspective. We tried to answer the following questions; When were the first useful drug molecules synthesized? Which types of glucocorticoids were first introduced to dentistry? Which types subsequently entered dentistry, and in which areas are they used in dentistry today?

During this project we have used scientific papers, patents and books from 1938 to present time. Some papers of scientific merit have been difficult to obtain and every citation is found in the reference list. We thank the staff at the University of Oslo Library located at the Faculty of Dentistry and the Library at the Royal Society of Medicine, London, UK, for excellent and kind help with obtaining relevant literature.

Finally we would like to express our gratitude to our mentors Professor Lasse Ansgar Skoglund and University research fellow Ellen Christine Vigen for patience, assistance and support through this project.

The introduction, synthesis and use of glucocorticoids in general medicine

Philip Hench specialized in arthritic diseases at the Mayo Clinic at St. Marys Hospital in Rochester, Minnesota. In April 1929 he observed a patient that was painfully affected with rheumatoid arthritis develop yellow jaundice (1, 2). Within a week most of his arthritic manifestations had disappeared. The jaundice lasted five weeks but the patient's arthritic symptoms did not relapse until several weeks after the jaundice had disappeared (1, 2).

Rheumatoid arthritis had for many centuries been considered a relentless progressive disease. Occasional remissions had attracted the attention of other writers such as Garrod in 1876, Osler in 1892, Still in 1897, Wishart in 1903, and Jones in 1909 (1-3). But relative complete remissions were so uncommon or so unpredictable that they were regarded as medical curiosities (1-3).

During the years 1929 to 1934, observations were made of 16 patients with chronic arthritis or fibrositis, who developed different types and degrees of jaundice. If the jaundice was severe enough, the rheumatic symptoms quickly diminished or disappeared for differing periods of time and then gradually returned (2-4). He then concluded that rheumatoid arthritis must be a potentially reversible disease, contrary to the belief held for centuries (2, 5, 6).

Hench and his colleagues at the Mayo Clinic gave volunteers suffering from arthritis various substances of the liver to try to identify this unknown substance, named "substance X" (5). Tests with bile salts, ox bile, human bile and liver extracts had no significant antirheumatic effect. They also injected highly jaundiced blood to arthritic volunteers, which led to a transient relief of symptoms (2, 3, 7). The ameliorating effect of jaundice lasted several weeks after the values of serum bilirubin in blood had returned to normal, so it did not seem likely that bile pigments were responsible (2).

The ineffectiveness of the various substances they tested strengthened an earlier suspicion that the antirheumatic "substance X" might be an extrahepatic substance found or activated elsewhere than in the liver as the indirect result of jaundice. Further, they concluded that "substance X" might be some substance not necessarily related to jaundice (2).

The researchers observed the same beneficial effects in rheumatoid women who became pregnant. Not long after the onset of pregnancy, an undramatic and slowly progressive development of relief from their arthritic disability was observed (1, 2, 4). Over a period of eight years (1931 to 1938) they studied this phenomenon as it developed twenty-four times in twenty women (5).
They therefore assumed that this unknown "substance X" of pregnancy was closely related to or perhaps identical to that of jaundice (2, 4).

One of the major biologic changes related to pregnancy is an increase in the bodily concentration of certain hormones. They therefore began to suspect that this mysterious substance was neither a product of the liver nor a female hormone, but might be a steroid hormone common to both men and women (2, 5, 8). This was strengthened by the knowledge that temporary remissions of rheumatoid arthritis frequently were induced by procedures known to be capable of stimulating the adrenal cortex, such as general anaesthesia and surgical procedures (8).

AMELIORATION BY PREGNANCY OR JAUNDICE

Conditions	Relieved by	
	Pregnancy	Jaundice
Rheumatoid arthritis	+	+
Chronic arthritis with psoriasis (skin unrelieved)		+
Psoriatic arthritis (skin unrelieved)	+	++
Psoriasis (no arthritis)	++	
Intermittent hydrops, "true"	+	
Intermittent hydrops, symptomatic, with rheumatoid arthritis	+	
Fibrositis, primary	+	+
Asthma	++	++
Migraine	++	+
Hay fever	++	+
Addison's disease	++	
Myasthenia gravis	++	

\+ Cases encountered by P.S.H.
++ Cases reported by others.

Figure 1 Results from "The potential reversibility of rheumatoid arthritis" (1)

Hench and his colleagues also observed that pregnancy and jaundice sometimes relieved a number of other conditions, particularly certain allergic conditions, such as hay fever, asthma, migraine and sensitivity to certain foods (2, 5). This was also observed in patients with psoriasis, Addison's disease and myasthenia gravis (2). The phenomenon of relief by the hypothetical common denominator of jaundice and pregnancy came to be regarded as group specific rather than disease specific (2).

Hench sought out help from various colleagues. Edward C. Kendall, head of the Division of Biochemistry at the Mayo Foundation, was from 1938 Hench's

chief collaborator. Between 1938 and 1948 they worked together and tried to find out what the chemical nature of "substance X" might be (2, 5, 6).
At the time none of them knew that Kendall and his associates who were working on the adrenocortical compound E in the laboratory, were actually trying to isolate, identify and synthesize "substance X" (2, 5).

In 1929, the first investigations that contributed to the development of cortisone came from physiologists (6). Two groups of workers, Hartman and his associates at the University of Buffalo, and Swingle and Pfiffner at Princeton University, were the first to prepare extracts from the adrenal cortex. These extracts successfully controlled the symptoms of adrenal insufficiency both in adrenalectomized animals and in patients with Addison's disease (6).
Kendall made attempts from 1930 to isolate, identify and synthesize the unknown hormones of the adrenal cortex. This was the last of the ductless glands to yield its secrets to its investigators (9).

They had tremendous difficulties with this problem, and from the beginning there was added an ever-present tension, because other chemists had chosen the same objective. A scientific race began, the chief participants being Wintersteiner and Pfiffner, at Colombia University, Reichstein and associates, in Zurich, Switzerland, and Kendall, Mason, McKenzie and Mayers, of the Mayo Foundation (5-7).

During the first 4 years of the 1930s, Kendall and his associates separated a small amount of crystalline material from the adrenal cortex, which turned out to be a mixture of several closely related compounds. The chemical nature and physiological effects were at the time unknown, and the role of the adrenal cortex in health and disease long remained obscure (5, 9). In 1934 the first crystalline compounds were separated, which Kendall named "compounds A, B, C and D" (10).

In 1935 the participants in the scientific race made many interconnected discoveries (6). Twenty-nine compounds were in all separated, but still only in relatively small amounts, inadequate to give to human beings. For Kendall, and Reichstein, and their associates, it took 10 years (1930 to 1940) to separate and identify these compounds (5, 6).

The laboratory of Professor Tadeus Reichstein in Zurich, Switzerland, made very significant contributions for the detailed investigation of this large group of compounds (6). In 1934 he began his research on the adrenal extracts with his colleague Joseph von Euw. As soon as it was possible to perform the first degradation experiments it became apparent that they were dealing with steroids, and they were able to prove this shortly afterwards (11, 12).

They isolated 29 steroidal substances, and all of these were closely related. Of these, five were already known: cholesterol, allopregnanolone, progesterone, oestrone and androstenedione. These occur in other natural substances, the rest were characteristic of the adrenals (11, 12).

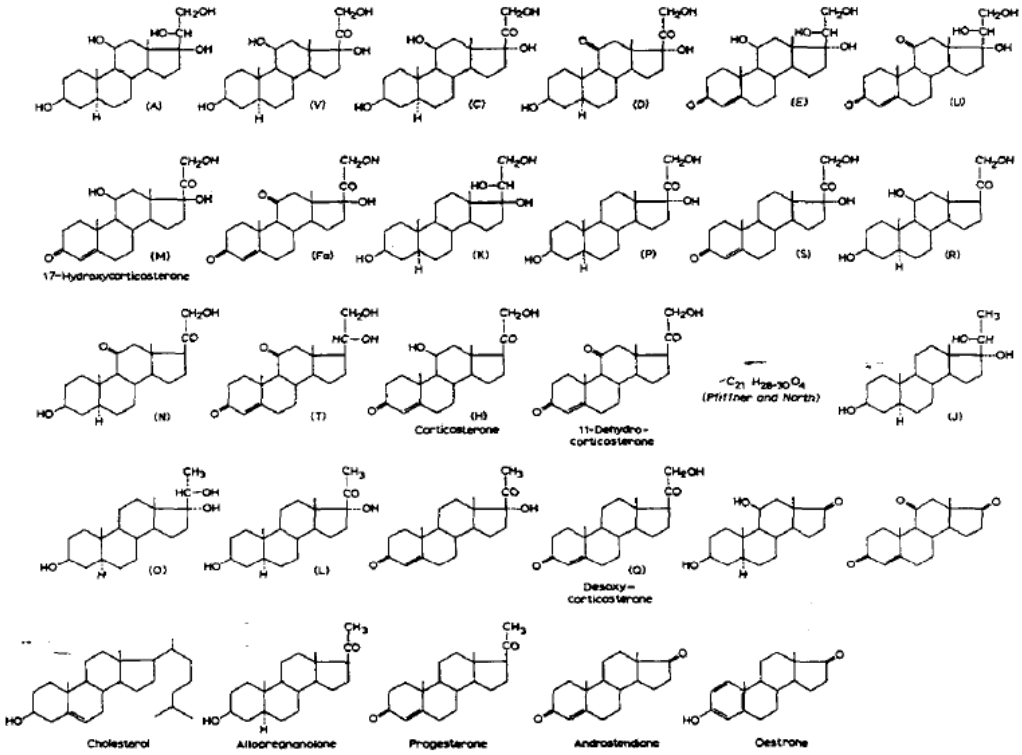


Figure 2 The 29 steroids isolated by Reichstein and Shoppee (12)

Of these 29 steroids, 6 were biologically active in the sense that they prolonged the life of adrenalectomized animals and were able to eliminate one or more of the deficiency symptoms (severe fatigue, chronic exhaustion, depression, weight loss, drop in blood pressure, disturbed salt levels in the blood etc.) (11, 12). The six steroids are 11-desoxycorticosterone, 11-deoxy-17-hydroxycorticosterone, 11-dehydrocorticosterone (Kendall's compound A),

corticosterone (Reichstein's substance H; Kendall's compound B), 17-hydroxy-11-dehydrocorticosterone (Reichstein's substance Fa; Wintersteiner and Pfiffner's compound F; Kendall's compound E; known today as cortisone), and 17-hydroxycorticosterone (Reichstein's substance M; Kendall's compound F - known today as hydrocortisone) (5, 11, 12).

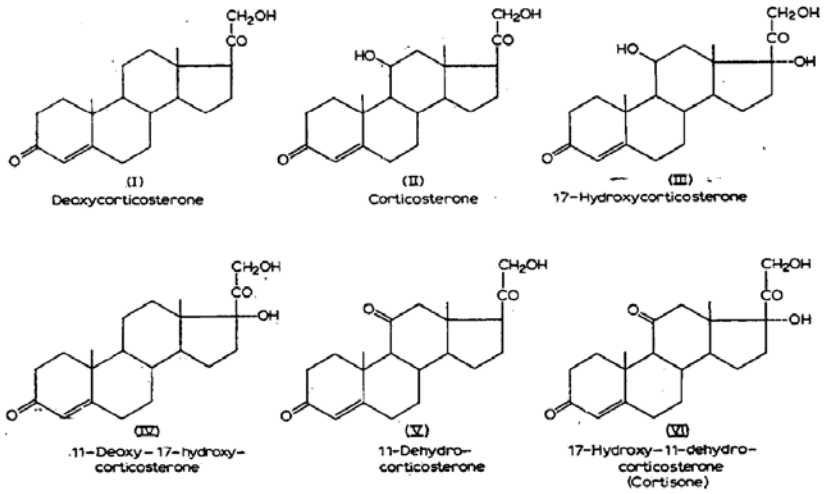


Figure 3 The 6 biologically active compounds found by Reichstein and Shoppee (12)

Reichstein's laboratory showed that, in the life maintenance test, and in the effectiveness on the electrolyte and water metabolism, desoxycorticosterone was by far the most effective, and 17-hydroxy-11-dehydrocorticosterone (compound E) and 17-hydroxycorticosterone (compound F) the weakest. In other tests, such as those connected with changes in carbohydrate metabolism, the relationship was reversed, and 17-hydroxy-11-dehydrocorticosterone (compound E) and 17-hydroxycorticosterone (Compound F) was the most effective (6, 11-13). The presence of an oxygen atom at C11 appeared to be essential for activity in regard to carbohydrate metabolism (11). A hydroxyl group at C17 increased the effect, but only as long as the oxygen atom at C11 was present (11). No natural steroid derivative certainly carrying oxygen in the 11-position was known before the discovery of the corticosteroids (11, 12).
It was also shown in experiments with mice and rats that compounds A, B, E and F had marked effect on the metabolism of protein, on muscular activity, and that

it increased physiological resistance to stress, cold, and to toxic substances such as typhoid vaccine (6, 10, 13).

It was impossible to separate enough material from the glands of animals for practical use. They were so limited in amount that they could not be used in human beings (6, 9). For the synthesis such substances first had to be artificially prepared. Reichstein and Steiger first achieved partial synthesis with 11-desoxycorticosterone in 1937. This was achieved starting from desoxycholic acid (6, 7, 12). But for practical purposes it was too laborious, as physiologists and physicians later demanded ever-greater quantities for research and clinical use. American research workers, particularly Kendall, developed better methods (7, 12).

On the basis of experiments on animals they speculated that the hormones from the adrenal cortex might be useful in the treatment of shock, traumatic injuries, burns, and some types of infection (6, 9). But when this hypothesis was tested with extracts of the adrenal cortex encouraging results were not obtained. For many years there were few who believed that any product of the adrenal cortex would find a place in clinical medicine other than in the treatment of the relatively few patients with Addison's disease (6, 9). Under these circumstances pharmaceutical manufacturers were not interested in the commercial aspects of the adrenal cortex (6). But in October 1941, the situation changed (6). The rumour that the pilots of the German Luftwaffe were injected with extracts of the adrenal cortex and that this allowed them to fly at ease at an altitude of 40 000 feet or more, induced a great stimulus to work on the adrenal cortex (6, 10). Twenty-two laboratories in the United States were in 1941 engaged with work related to the laboratory preparation of the hormones of the adrenal cortex (6).

It became necessary to find a method that could be used to prepare these hormones of the adrenal cortex by partial synthesis from some material that could be obtained on a large scale. No chemical so complex had ever been made by man artificially, so this was the most difficult part of all (6, 7, 9). It was decided that the objective should be compound A, the next more complicated structure after 11-desoxycorticosterone (6). Lardon and Reichstein, in

Switzerland, prepared the first sample of compound A from desoxycholic acid but the method could not be used on a large scale (6).

During the years 1940-44, a suitable procedure for large-scale production of 11-dehydrocorticosterone (compound A) was devised in Kendall's laboratory. In 1946 Dr. L. H. Sarett in the research laboratory of Merck & Co., Inc., prepared a large sample of compound A by this method (5-7, 9), but when given to a patient with Addison's disease it proved to be of little value. Interest in the hormones of the adrenal cortex sank to a very low level (6, 10).

In 1946 it was generally believed that compounds A, B, E and F closely resembled each other in physiological activity (6). There was at the time no conclusive evidence that compound E was qualitatively different from compound A, and there was therefore no assurance that large-scale production of compound E was worthwhile (6, 9).

In spite of the disappointing results, they determined to make a small sample of compound E as a compromise. Sarett discovered a new procedure to convert a closely related product of compound A into compound E, by addition of one more step that resulted in hydroxylation at position 17 (6, 7). In May 1948 they had a few grams of compound E available, and more was produced during the summer (5, 6, 9, 10).

Merck & Co., Inc. held a conference with a group of clinicians to consider how the material should be used (9). The first supply compound E was given to endocrinologists who found it useful in Addison's disease. But this condition was so rare that it alone did not justify continued production (5). They decided that unless some wide demand for compound E developed, they would not make more of this hormone (9).

Kendall and Hench had on one of their conferences in January 1941, decided that compound E should be used for patients with rheumatoid arthritis whenever it might become available (2, 6, 7, 9). Kendall had remarked on one of their conferences that his compound E increased the resistance of animals against reactions to typhoid vaccine. They did not realize at the time that seven years would pass before compound E would become available in amounts sufficient to permit use in clinical medicine, but neither of them forgot the

decision made in 1941 (2, 6, 7, 9). Even though it was available in May 1948, it was not employed until September of the same year (9).

Dr. Slocumb, Hench's associate, began on September 21, 1948, to administer the first injection of compound E to a 29-year-old woman with severe rheumatoid arthritis of 4-5 years duration (2, 6-8, 13). They began with a daily dose of 100 mg intramuscularly (2, 5-7). The patient was markedly improved within three days and continued to improve until the daily dose was reduced to 25 mg (2, 7). After only a week with daily administrations of compound E, articular as well as muscular stiffness had almost disappeared, and tenderness and pain on movement, and even swellings, were markedly reduced (8, 13). The antirheumatic effect was unlike that of any previous remedy, or of any agent, and resembled the effects of pregnancy and jaundice (5). Only four more patients were given compound E from September 1948 to January 1949, because of limited supplies (2).

A supply of ACTH was requested, in January 1949, from Dr. John R. Mote, director of laboratories of Armour & Co. It had taken other scientists 13 years (1933 to 1946) to isolate and prepare this hormone (2, 5). On February 8, 1949, they first administered it to a patient with rheumatoid arthritis (2). After this first administration, compound E, or ACTH, or both were given to a series of patients with severe rheumatoid arthritis (2, 6). Hench, Kendall, Slocumb and Polley presented the first report of results April 20, 1949 (2, 8).

The effect of compound E on rheumatoid arthritis and rheumatic fever were widely spread in medical journals, newspapers, magazines and over the radio (9). As a result of these convincing trials, there was some confusion concerning the relation between vitamin E and compound E of the adrenal cortex, in the minds of the public. It was therefore desirable to give compound E a distinct name, and cortisone was chosen (6).

Most symptoms were markedly and quickly reduced in practically all cases during the use of either hormone (2). Clinical results from ACTH were essentially similar to those from cortisone (5). They assumed that ACTH stimulated patients with responsive adrenals to increase production of their own cortisone, or a similar steroid hormone such as compound F (hydrocortisone) (2, 6).

When either hormone was given, they first observed a reduction of the subjective symptoms (stiffness, soreness and tenderness). They later observed a reduction of the objective symptoms (fever, swelling, size of rheumatoid nodules and enlarged lymph nodes). The patients commonly developed a sense of well-being, increased psychomotor activity, and increased appetite and weight (2, 8).

It was observed that the signs and symptoms of rheumatoid arthritis usually returned when the use of these hormones were discontinued (8). The symptomatic relief usually lasted as long as the hormones were given. Relapses generally occurred thereafter, usually within one or two months, occasionally more severely (rebound relapses) (2, 14). This indicated that the disease was suppressed rather than cured (2, 7).

A close relative of cortisone, 17-hydroxy-corticosterone, was prepared in the research laboratories of Merck & Co., Inc., in 1950 (7). First called compound F and now designated hydrocortisone (7). Hench and Kendall had in March 1949, obtained just enough of this hormone to use for 12 days on one patient. The effects of compound F were comparable to those of compound E and ACTH (5). Hench and Kendall suggested that these hormones might be useful against other rheumatic and non-rheumatic conditions, which are relieved by pregnancy and jaundice (8).

In 1949 Hench and Kendall administered cortisone to 3 adolescent patients with acute rheumatic fever (15). There was in each of these cases a rapid disappearance of fever, tachycardia and polyarthritis, and a reduction of the elevated sedimentation rates and abnormalities in the EKGs (15). The same result was obtained with the use of ACTH (2). Although the hormones suppressed the symptoms, they did not "cure" rheumatic fever. But with proper use the hormones seemed to protect the heart from damage (2, 7).

When given to patients with lupus erythematosus, psoriasis, pemphigus and ulcerative colitis encouraging results were seen (2, 9). Several types of allergic conditions such as hay fever, bronchial asthma, status asthmaticus, infantile atopic eczema, urticaria and certain skin and other reactions due to penicillin, gold and other drugs, were shown to be suppressed by the use of these hormones (2). These hormones were also shown to be useful against the acute and subacute inflammatory diseases of the eye (2). More than 25 clinical

syndromes were shown to be influenced by cortisone, and it seemed improbable that all of these conditions were caused by a lack of cortisone (13).

The wide application of this hormone came as a surprise to many of those interested (6). And it produced a situation that was quite different from the sequence of events associated with the isolation and use of the hormones from other glands of internal secretion, i.e. adrenalin, insulin etc. There was no one that had shown that an extract of the adrenal cortex could influence the symptoms of rheumatoid arthritis, rheumatic fever and asthma (6).

Hench and Kendall had in 1941 given the adrenal extract, cortin (whole adrenal extract), to certain arthritic patients, but the results were not impressive (2, 5). When it was shown that cortisone possessed unusual physiological activity not associated with any known function of the adrenal cortex, it was a tendency to regard cortisone as a pharmaceutical agent rather than as a hormone of the adrenal cortex (6). This led many investigators to believe that many other compounds would be found which were as good as or better than cortisone. This tended to remove cortisone from its rightful place as a hormone (6).

These hormones had shown outstanding and unique clinical results in rheumatic, allergic, and collagen diseases conditions (2). Investigators concluded that the effect of these hormones seemed to be group specific. But how these hormones accomplished their effect was at the time still quite unknown. They did not kill germs or appear to remove the unknown etiologic irritants of the conditions they had effect on. Thus they did not "cure" the diseases; they only modified the symptoms profoundly (2). They seemed to provide the susceptible tissues with a shield-like protection against a variety of irritants (2, 7).

It had been shown that cortisone could modify the effect of a large number of chemical irritants and protein antigens (7). And they thought it possible that cortisone could cause a remission in the symptoms of rheumatoid arthritis by protecting the tissues from such antigens, or from the effect of the products formed by a combination of an antigen with an antibody (7). What physiological processes that were modified by cortisone and how this influence was employed were at the time still unknown (6).

Practically 100 % of patients with active rheumatoid arthritis responded in some degree to the administration of cortisone (7). It was observed that long-term use of large amounts of cortisone had certain undesirable effects on the patients (7, 9, 14).

The side effects observed were related to the dose of cortisone and to the sex and age of the patients. Men were less prone to side effects than women (7, 14). Side effects encountered frequently were mild irritability with increased psychomotor activity, an initial retention of sodium chloride and water producing fluctuant weight, mild hypertrichosis, acneiform eruption, irregularity of the menstrual cycle, and rounding of the face (2, 14).

The clinical researchers also encountered certain rare side effects, such as transient renal glucosuria or significant reduction of carbohydrate tolerance; hypopotassemic hypochloremic alkalosis; transient major alterations of psyche, generally in persons with markedly disturbed personality patterns; and spontaneous fractures occurring in elderly osteoporotic persons (2). Significant interference with wound healing also occurred in some patients receiving the usual doses (2). It was also noted that cortisone suppressed the activity of the adrenal cortex. When cortisone was administered in large amounts over a long period, atrophy of the adrenal cortex would appear (9). But all these side effects were reversible and would disappear when dosage was lowered or the use of cortisone was discontinued (2, 9, 14).

Because of their potential effects, they advised that cortisone and ACTH should be used with caution in relation to certain diseases such as hypertensive cardiovascular disease, diabetes mellitus, tuberculosis, latent or frank psychoses, marked osteoporosis and peptic ulcers (2).

In some patients they observed a post-cortisone withdrawal syndrome, with severe malaise with depression, fatigability, anorexia and weakness (14). As an essential precaution they therefore advised a gradual withdrawal of the hormone (14).

Cortisone was made available to every physician and research worker of the United States through drug supply houses, on November 1, 1950, thanks to Merck & Co., Inc (5, 6).

In 1950 Hench, Kendall, and Reichstein won the Nobel Prize in medicine for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects (2, 6, 12).

The introduction and use of glucocorticoids in dentistry

The use of cortisone in dentistry started in the early fifties. Hench and his associates revealed in 1949 the most important information the medical world has received in relation with pituitary and adrenal cortical hormones. The basis of the use of these newly discovered hormonal substances developed from their specific anti-inflammatory action (16). The hormone was at first used by intramuscular injection, then later in tablet form per orally, subconjunctivally in the eye, topically on the skin and other epithelial tissues, and intra-articularly in joints (16).

Since the use in medicine mainly started with rheumatic patients, this continued in dentistry with temporomandibular injections in patients with trismus (17-19). However scientists soon saw possibilities in other dental specialties where inflammations were a common problem (16).

Thorn was one of the first scientists to inject hydrocortisone into the knee joint, and the patient treated noticed an immediate effect (17). Researchers hoped that a similar effect would be evident in the mandibular joint. Lyon P. Strean was one of the first scientists who started experimenting with the general use of the hormones in dentistry (16). He had noticed that a systemic administration wasn't always successful in all joints, and wanted to get a higher local dosage without the side effects of systemic administration. He injected hydrocortisone into the upper chamber of the mandibular joint of five patients with limited motion of the mandible (18, 19).

One of his patients had a vertical opening of 2 cm and had such limited movement of the mandible that he had to live on a liquid diet. After the injection of 0.5 cubic cm of hydrocortisone acetate the patient had a vertical opening of 5 cm. Although there was a need of several later injections, this was a great improvement. The other four patients also showed an improvement in vertical opening (19).

In each of the five patients treated the pain disappeared, the swelling subsided and movement was increased within 72 hours. Freedom from subjective symptoms lasted several weeks, in others several months (18, 19).

Strean presented other uses of the hormones as well, in fields where inflammation was a problem.

Within the endodontic field of dentistry Strean's focus was on the apical periodontitis that can occur after a pulpectomy. He wanted to se if he could reduce the post-treatment apical inflammation by pumping hydrocortisone apically through the cavum after treatment. In ten cases he found a positive effect, with no postoperative inflammation (18, 19).

He also tried hydrocortisone ointment locally for gingival inflammations. For both desquamative gingivitis and gingival hyperplasia on epileptic patients, this had a good effect. In areas with food impaction and restorations with overhang the application of cortisone also led to an improvement on the inflammation, but Strean emphasized that this was not a cure and that the causative agent had to be removed in such cases (18, 19). Strean kept on researching the effects of cortisone and hydrocortisone, resulting in a book published in 1957: "Cortisone in dentistry" (20).

In 1953 Staple demonstrated the inhibition of fibroblastic proliferation of cortisone, and used it in cases of severe gingival hyperplasia resulting from Dilantin therapy for epilepsy. He concluded that topical application of hydrocortisone could prevent recurrence of gingival hyperplasia after surgery (16).

Other uses of cortisone and hydrocortisone was also explored and studies in the beginning of the 1950s indicated that these hormones were of value in the treatment of many diseases of the oral mucosa. Including angular chelilitis, oral lichen planus, chronic desquamative gingivitis, lupus erythematosus, pemphigus and aphtous stomatitis (16).

Wolfsohn published results on the use of hydrocortisone acetate in the field of endodontology in 1954 (16, 21, 22). In his research in the treatment of root canals for the control of apical periodontitis, he concluded that the hormone resulted in "the reduction and elimination of severe secondary inflammatory reactions in the periodontal membrane following treatment" (21). When used in the presence of an infected pulp and infected periapical tissue, he found that the drug appeared to produce exacerbation of the disease process. He therefore

concluded that the pulp canal had to be rendered sterile prior to the introduction of hydrocortisone (16, 21, 22).

Rapoport, Irving and Abrahamson wanted to improve the technique of pulp-capping and pulpotomy procedures by using hydrocortisone acetate (23). According to their article, the problem with an inflamed pulp was that it would lead to an increased vascular pressure that would spread to the apical area and in the end stop the blood flow to the tooth. The goal of their treatment was that hydrocortisone would reduce the inflammation and vascular pressure, thereby giving the pulpal tissue continued blood flow and an increased possibility to survive. They concluded that the use of hydrocortisone leads to a higher degree of success, although there was no statistical significance to their results and they lacked a control group (23).

Strean had briefly mentioned the use of corticosteroids after extractions in an article from 1952 (18), but little else is to be found until an article published in 1958 (24). In the field of oral surgery Ross and White saw the problem with post-surgical inflammations. In this article they describe the anti-inflammatory mechanisms of hydrocortisone. Hydrocortisone is said to "alter the activity of the injured tissue cell so that it becomes less capable in liberating the chemical agents involved in producing the phenomena of inflammation" (24).

Ross and White did a double-blind study on 61 patients going through removal of impacted or partly impacted 3rd molars, giving over half the group hydrocortisone orally. The experimental group received 40 mg of hydrocortisone twice a day preoperatively, 40 mg four times a day on the day of surgery and 40 mg twice a day postoperatively the two following days. Edema, pain, trismus and wound healing was observed and compared to the level of trauma during surgery.

A statistically significant reduction in edema was found. A reduction in both pain and trismus was also observed, but not statistically significant.
The authors used hydrocortisone instead of cortisone because the former had a slightly higher potency requiring only 80 % of the dosage of cortisone (24). However, there was some uncertainty whether cortisone could harm the healing process (24, 25). In a clinical trial by Shafer 65 rats were included Thirty-five rats received cortisone acetate on the day of surgery and the following days (25).

Shafer found no evidence of retardation of the healing process until the tenth day. Continued use lead to lack of maturation of granulation tissue and lack of re-epithelialization, but had no interference with bone formation (25).
Ross and White therefore deemed it safe to use hydrocortisone in their study (24).

After the introduction of other synthetic analogues of cortisone and hydrocortisone, they were soon tested for their usefulness in dentistry. These analogous include prednisone, prednisolone, dexamethasone and betamethasone. Several investigators found that these steroids also could reduce the incidence and severity of some sequelae of dental and oral surgery. Especially noteworthy was the reduction in post-operative edema or swelling by steroids.

In 1960 Freedman published an article where he tested the combination of prednisolone and vitamin therapy in 124 patients undergoing multiple extractions (27). The test group received a combination of prednisolone, citrus bioflavonoid complex and ascorbic acid. All groups showed swelling, but the group receiving the study medication had a more rapid reduction in their edema than the control group. Additional side effects of trauma including soreness, pain and eccymosis were also reduced (27).

Linenberg and Westfield did a clinical evaluation of dexamethasone in oral surgery, published in 1965 (28). They emphasized the need of reducing edema, cellulitis and trismus following oral surgical procedures. In traumatic cases one has to wait for the edema to abate before initiating treatment, because the body's response is so great, and therefore valuable time is lost. They included 120 patients in their study, and in all experiment they had control groups. In cases where surgery needed to be performed bilaterally, dexamethasone was employed on one side.
In their study Linenberg and Westfield concluded that whenever dexamethasone was used in the treatment of cellulitis, the duration of treatment was considerably lessened. Post-operative edema was practically eliminated following removal of impacted third molars and full-mouth alveoloplasty, and trismus was also lessened. In patients with facial fractures they emphasized that dexamethasone had to be administered within 1 to 3 hours after the fracture to

be useful. Once edema was evident, dexamethasone would only impede its increase. In this study dexamethasone was only administered for 2 days, so no side effects were noted in any of the patients receiving dexamethasone, including the patients with diabetes mellitus and stomach troubles (28).

In a study published in 1964, Nathanson and Seifert did a double-blind study to investigate the usefulness of betamethasone in oral surgery (26). They found that more treated than non-treated patients were entirely free of pain on the third day, although the difference was not remarkable. But the most impressive effect was on the incidence and degree of edema. 82 % of the patients that received betamethasone did not have this symptom at all on the third post-operative day. There was no significant difference in trismus on the third post-operative day in the two groups. In this study they also noticed that in some patients that received betamethasone, edema was present immediately after the surgical procedure but subsided later in the day. Betamethasone is absorbed around 4 hours after oral administration, and is therefore consistent with their observations.

Nathanson and Seifert believed that betamethasone promotes healing of the traumatized tissues, because of the reduction in incidence and extent of post-operative sequelae. This clinical study in humans did not reveal any clinical evident side-effects of betamethasone, because of its short duration of administration (4 days). The authors emphasized, however, that in the presence of infection in the oral cavity, steroids should only be used if antibiotic agents are administered concurrently (26).

How do glucocorticoids reduce inflammation?

Glucocorticoids are widely used drugs to reduce inflammation (29). Not only does it affect the early stages of inflammation like edema, redness and pain but also later stages of healing and repair. Whether the cause is an infection, trauma, graft versus host reaction or chronical, the drug reduces the inflammatory reaction (29). The working mechanism of glucocorticoids is complicated. The effect is two-fold; both genomic and non-genomic (30).

The genomic mechanism

The genomic effect works by acting directly on the gene expression, and thereby changing the cell production (29-31). Glucorcorticoids, either natural or synthetic, enter the cell and binds to a lipophilic glucocorticoid receptor (cGCR) in the cytosol. The cytosol contains a protein complex with heat shock proteins and immunophilin together with cGCR, and by binding the glucocorticoid or a glucocorticoid analogue to cGCR, the receptor changes its conformation and is released from the group.

After the conformation is altered, the receptor also exposes a DNA binding domain (29-31). The role of the heat shock protein is to work as a chaperone (32). The chaperone protects the cGCR and keeps it in place when it is unoccupied (32). The transportation to the nucleus may be by the cytoskeleton, although first after a conformation to a homodimer (29). This is however not fully delineated (29). The genomic effect on the cell production is both by transactivation and transrepression (30). Transactivation means that a cGCR complex binds to a glucocorticoid response element (GRE) in the nucleus and affects the protein production (29, 30).

The transactivation results in an increased production of anti-inflammatory and regulatory proteins, meaning annexin-1, interleukin-1 and also an inhibitor of nuclear factor κB (30). Although this effect is important, the transrepression effect is most likely the most important in reducing inflammations. The complex of cGCR and glucocorticoids binds to transcription

factor subunits, and will compete with factors regulating the transcription of pro-inflammatory genes for cytokines such as IL-1, IL-2, TNF and INFγ and also prostaglandins (30). It is believed that approximately 1% of the genes may be regulated by steroids (29). Figure 4 shows the genomic mechanism of glucocorticoids (30).

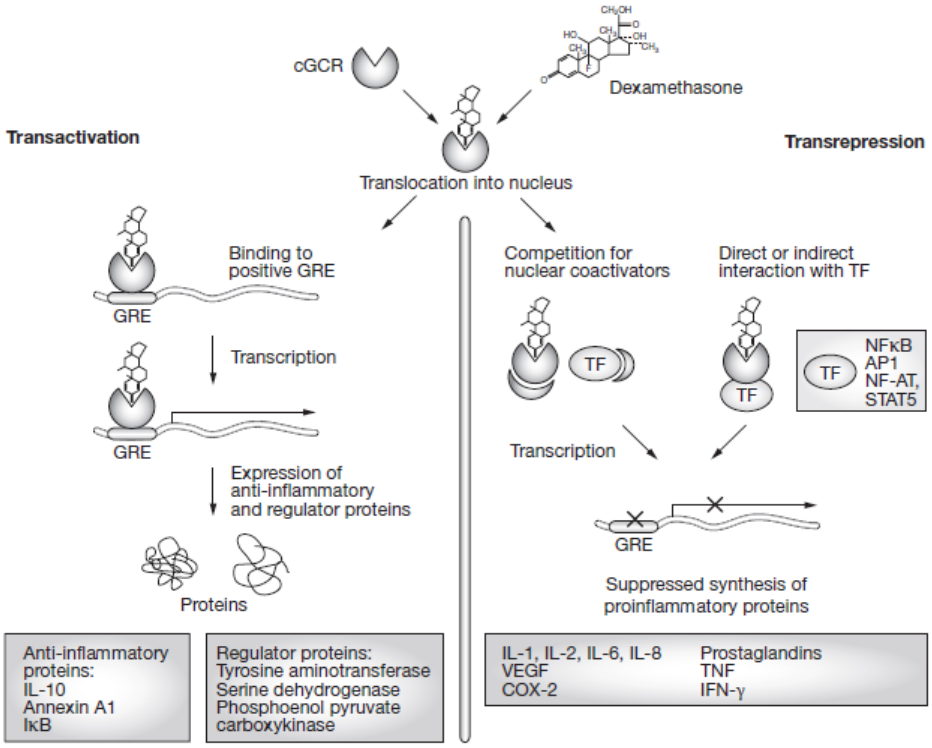


Figure 4: The genomic effects of glucocorticoids include transactivation and transrepression. Binding of the glucocorticoid–cGCR complex to GREs leads transativation by altering the expression of anti-inflammatory and regulatory proteins such as IL-10 or IκB. Transrepression, a suppressed synthesis of proinflammatory proteins, is caused by competition for nuclear coactivators, or direct or indirect interaction with transcription factors.

Abbreviations: AP1, activator protein 1; cGCR, cytosolic glucocorticoid receptor; COX-2, cyclooxygenase 2; GRE, glucocorticoid response element; IκB, inhibitor of NFκB; IFN-γ, interferon γ; IL, interleukin; NF-AT, nuclear factor of activated T cells; NFκB, nuclear factor κB; STAT5, signal transducer and activator of transcription 5; TF, transcription factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. (30)

The nongenomic mechanism

The nongenomic effect of glucocorticoids is what causes the direct and rapid effect (30). Stahn and Buttgereit suggest several effects; interactions with cellular membranes, effects due to the cGCR and an effect caused by a membrane bound glucocorticoid receptor (mGCR). The cell membrane interaction is mainly on plasma and mitochondrial membranes. Glucocorticoids in higher doses

(>30mg prednisone per day) can change the physiochemical barrier and thereby change the function of several important membrane bound proteins.

The reduced inflammatory effect is caused by an altered calcium and sodium cycling across the membrane of mitochondria and plasma cells. The affected membrane proteins may also cause an increased proton leak in mitochondria and inhibit oxidative phosphorylation, resulting in a reduced ATP production. Several important pro-inflammatory actions such as cytokine synthesis, phagocytosis, migration and antigen processing and presentation are highly dependent on ATP (30).

The cGCR is responsible for changing the transcription but it may also contribute to a direct effect. Binding of a glucocorticoid to the cGCR results in proteins dissociating from the complex that cGCR was bound to. These proteins may again inhibit release of arachidonic acid which is crucial in the production of several pro-inflammatory mediators (30).

Recent reports suggest the existence of a membrane bound receptor (mGCR) (33). The effect is yet unexplained, but binding of glucocorticoids to mGCR seems to inhibit T-cell receptor signaling (33).

The mechanism of glucocorticoids results in an anti-inflammatory effect on several levels (29-32). Cytokines are important regulators in an inflammation and when the transcription of many of these are inhibited by glucocorticoids, the reduced concentration of interleukin-1(IL-1), TNF-α, GM.CSF and several other interleukins will be evident on the inflammatory reaction (32). T-lymphocytes are stimulated by the activation of AP-1(transcription factor activator protein-1), which then again will induce target genes like IL-2 and the IL-2 receptor.

Normally TNF-α will activate AP-1 but this is counteracted by the glucocorticoids. The result is therefore a reduced stimulation of T-lymphocytes, an important cell in the inflammatory reaction (32). Decreased cell adhesion factors and cytokines will affect the outlet of neutrophils from blood vessels, and also reduce the activation of neutrophils and macrophages, which are very important cells in the inflammatory reaction (29, 31). Wound healing will slow as the fibroblast function is decreased, and also the production of collagen and glycosaminoglycan (29).

According to Yagiela et al. steroids reduce the level of Phospholipase A_2 (PLA_2) and cyclooxygenase-2 (COX-2) (31, 34). These are important enzymes on several levels in the inflammatory process. COX-1 is prevalent in most cells in the body acting as a "housekeeper" by regulating homeostatic functions. In an inflammation, however, COX-2 is assumed to be the most important COX-enzyme (35).

By reducing the production of COX-2 and PLA_2, the production of leukotrienes and prostaglandins is downgraded (29, 32). Free arachidonic acid is a necessary precursor, and PLA_2 is a rate-limiting step in the synthesis of this substance while COX-2 affects the further synthesis to prostaglandins. (36).

The leukotrienes act by causing adherence, chemotaxis and activation of polymorphs and monocytes, macrophages and lymphocytes are stimulated to produce cytokine, and also a vasodilation in the body's vessels except in coronary and bronchial muscles (37).

Prostaglandins affect vasodilation and platelet aggregation, and the generation of toxic oxygen metabolites from neutrophils will decrease (PGE_2, PGI_2)(38) .The effect is mainly in macrophages, monocytes, fibroblasts and endothelial cells (31).

The anti-inflammatory effect of glucocorticoids is very well documented in an article published by Newton et al. in 1997 (34). The research group stimulated an inflammatory response in human epithelial cells by adding the pro-inflammatory cytokines PMA, TNF-α and IL-1β to in vivo human epithelial airway cells. The mix is altogether called cytomix. By adding the cytomix to the different cultures they could register a substantial increase in both the levels of cytosolic PLA_2 mRNA and COX-2 mRNA. To observe the effect of corticosteroids they pretreated cells with dexamethasone before adding the cytomix. Results showed that the dexamethasone lead to a significant down regulation in both kinds of mRNA (34). Some research has also suggested that the effect of glucocorticoids on COX may also work by post-transcriptional regulation and thereby stabilizing the COX-2 transcript (39).

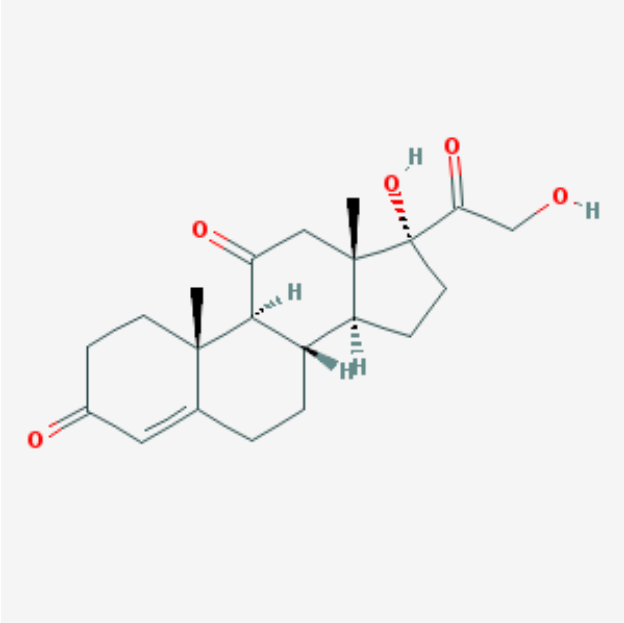
Possible effect on the nervous system

Through the last decades the effect by glucocorticoids on inflammation has been evident. However, recent research implies the effect not only on inflammatory substances but also an effect on the nervous system. Several reports have found a relation between the glucocorticoid receptor and NMDA (40-42). Some have found a neurodegeneration following a high level of glucocorticoid receptors in the central nervous system due to a receptor agonist (41).

Research by Couessens et al. suggests that the threshold of certain NMDA-receptors is lowered by the glucocorticoid receptor through voltage gated calcium channels (43). The working mechanism of glucocorticoids on the nervous system seems to be complicated and a lot is yet to be discovered (43).

Different types of glucocorticoids

Cortisone

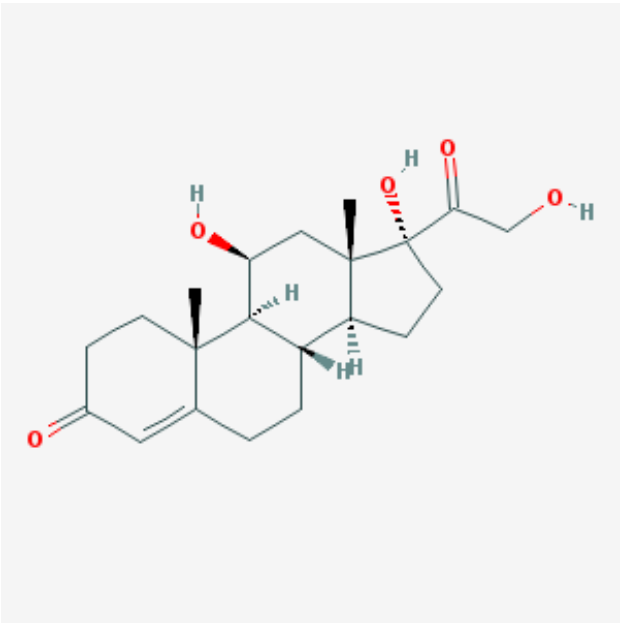


Molecular formula: $C_{21}H_{28}O_5$

Molecular weight: 360.44402 (g/mol)

(44)

Hydrocortisone

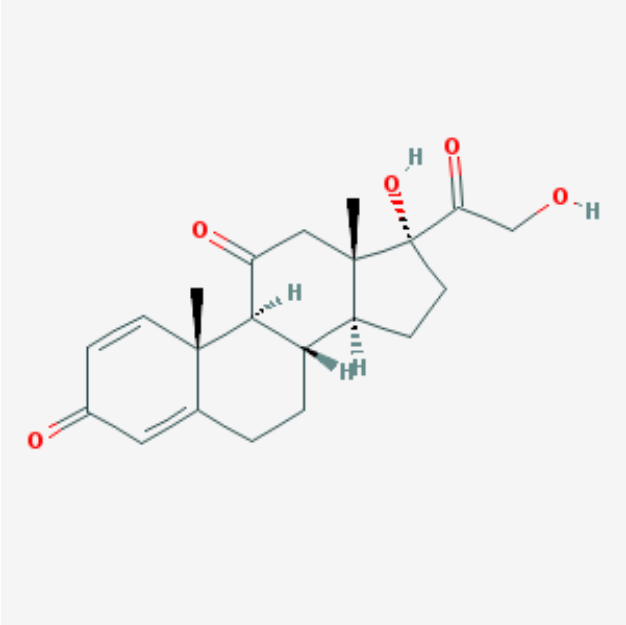


Molecular formula: $C_{21}H_{30}O_5$

Molecular Weight: 362.4599 (g/mol)

(45)

Prednisone

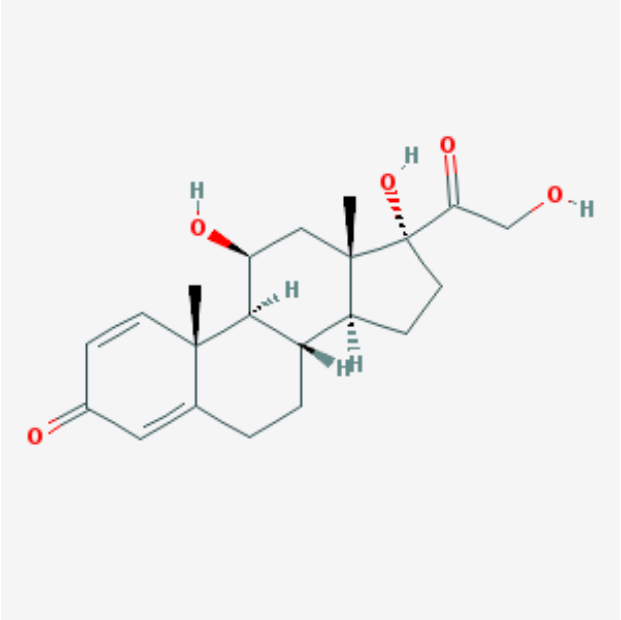


Molecular Formula: $C_{21}H_{26}O_5$

Molecular Weight: 358.42814

Prednisone is a synthetic anti-inflammatory compound derived from cortisone. It has no substantial biological activity until it is converted to prednisolone in the liver (46).

Prednisolone

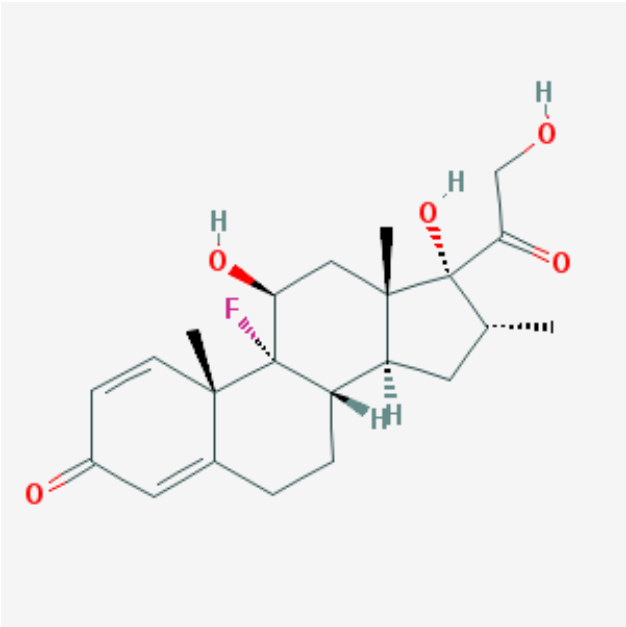


Molecular Formula: $C_{21}H_{28}O_5$

Molecular Weight: 360.44402

(47)

Dexamethasone

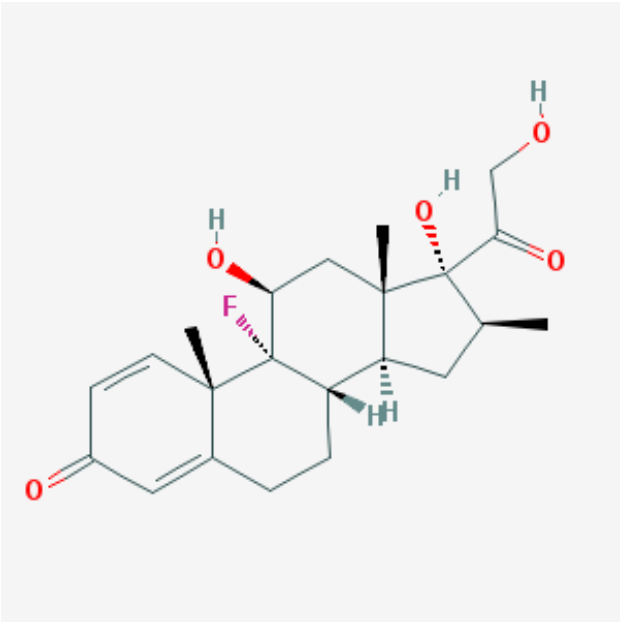


Molecular Formula: $C_{22}H_{29}FO_5$

Molecular Weight: 392.461063 (g/mol)

(48)

Betamethasone

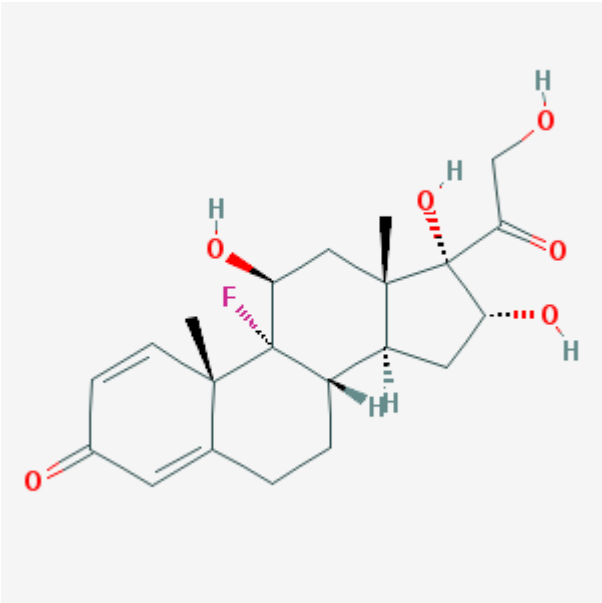


Molecular Formula: $C_{22}H_{29}FO_5$

Molecular Weight: 392.461063 (g/mol)

(49)

Triamcinolone

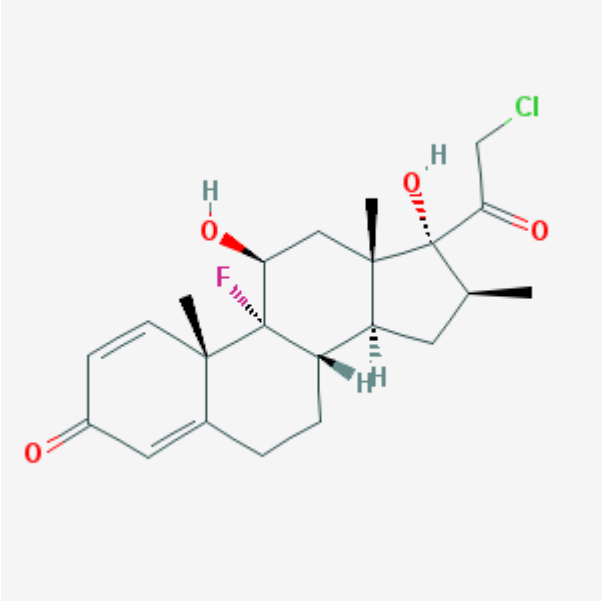


Molecular Formula: $C_{21}H_{27}FO_6$

Molecular Weight: 394.433883 (g/mol)

(50)

Clobetasol



Molecular Formula: $C_{22}H_{28}ClFO_4$

Molecular Weight: 410.906723 (g/mol)

(51)

First patents

Substance	Inventor	Applicant	Patent nr	Original Application	Patented
Prednisone and prednisolone	Arthur Nobile	Schering corp	US 2837464	Jan. 11, 1955	Jun. 3, 1958 (52)
Dexamethasone	Glen Edward Arth and David Johnston	Merck & Co., Inc	DE 1113690	Feb. 22, 1958	Sept. 14, 1961 (53)
Dexamethasone		Upjohn Co	GB 869511	May 26, 1958	May 31, 1961 (54)
Betamethasone	David Taub, Norman L. Wendler, Harry L. Slates	Merck & Co., Inc	US 3053865	Mar. 19, 1958	Sept. 11, 1962 (55)
Triamcinolone	Bernstein Seymour, Robert H Lenard, William S Allen	American Cyanamid Co	US 2789118	Mar. 30, 1965	Apr. 16, 1957 (56)
Clobetasol	Joseph Elcks, Gordon Hanley Phillipps	Glaxo Lab Ltd.	DE 1902340	Jan. 17, 1969	Sept. 11. 1969 (57)

Table of comparison (58)

	Potency relative to hydrocortisone			Half-life	
Substance	Equivalent Glucocorticoid dose (mg)	Anti-inflammatory	Mineral-corticoid	Plasma (minutes)	Duration of action (hours)
Cortisone	25	0,8	0,8	30	8-12
Hydrocortisone	20	1	1	90	8-12
Prednisone	5	0.8	0.8	60	12-36
Prednisolone	5	0.8	0.8	200	12-36
Triamcinolone	4	5	0	300	12-36
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	0.6	30	0	300	36-54
Klobetasol	NA	NA	NA	NA	NA

Common glucocorticoid drugs in use in Norway (59)

Systemic treatment:

- Hydrocortison – (Solu-Cortef)
- Betametason – (Celeston Chronodose)
- Metylprednisolon – (Depo-Medrol, Solu-Medrol)
- Triamcinolon – (Kenacort-T, Lederspan)

- Cortison
- Hydrocortison – (Plenadren)
- Dexametason
- Prednisolon – (Lodotra)
- Metylprednisolon – (Medrol)

Topical treatment

- Hydrocortison – (Mildison)
- Hydrocortisonbutyrat – (Locoid, Desonid)
- Betametason – (Betnovat)
- Fluocinolonatcetonid – (Synalar)
- Fluocinonid – (Metosyn)
- Klobetasol – (Dermovat)

Commercial names are presented in brackets ( ).

Glucocorticoids- the use today

With its anti-inflammatory action, glucocorticoids have proven to be a great asset in treating unwanted inflammations in several oral conditions (60). Patients suffering from temporomandibular joint pain caused by trauma, bruxism, rheumatoid arthritis or other causes may struggle with pain, discomfort and reduced mouth opening. In many cases where conservative measures did not prove successful, intraarticular injections of glucocorticoids are often attempted. Depending on the cause, the effect may be permanent or temporary, and the effect may only be partial. Cases where no radiographic changes are evident seem to be the best cases for this type of treatment (60).

Oral surgery is another field where glucocorticoids are used (61). The goal is to prevent postoperative sequelae, meaning edema, trismus and pain. The effect on edema is statistically significant, and research also shows a reduction in pain and trismus. A possible outcome is a reduced need of analgesic and antiemetic drugs (61). Short term use of steroids seems to have a very low risk of side effects, including no higher risk of infection (62).

Oral ulcerations such as traumatic ulcers, stomatitis, erosive lichen planus, pemphigus, erythema multiforme, desquamative gingivitis and aphtous ulcers may cause great discomfort to the patient (60). In these cases glucocorticoids are sometimes used as a palliative measure so that the patient can eat and talk without distress. The administration is either topical or systemic. If the clinician is suspecting a herpes infection, glucocorticoids should not be used. Glucocorticoids can suppress the host response, and thereby allowing the virus to spread (60).

In some endodontic cases glucocorticoid therapy has been attempted. The drug Ledermix is used by some dentists and is a combination of a tetracycline called demeclocycline and a glucocorticoid called triamcinolone (63). According to the producer Blackwell Supplies, there are several possible indications. The drug may be used as a temporary filling between RCT sessions and it can be used as a pulp capping or indirect pulp capping material. In cases of pulpitis where the cavity preparation causes exposure or near exposure of the pulp, and the pulpitis

is not purulent, this material may be used (63). However, there is no established efficacy of steroid treatment in such endodontic cases (60).

Glucocorticoids - future possibilities?

Treatment for sensory impairment

After orthognatic surgery sensory impairment is a common complication (64). Because of natural recovery, most cases need no treatment, but when the patient suffers for an extended time there is a possibility of secondary symptoms such as dysesthesia. In addition the patient often suffers from discomfort in eating, shaving and washing their face. Severe cases of sensory impairment are often treated with microneurosurgery, but the question is whether moderate cases should be treated with glucocorticoids.

Glucocorticoids have the recent years been used to treat several nerve injuries, such as spinal cord injuries, Bell's palsy and optic neuritis. The drug shows not only an anti-inflammatory effect, but also a neurotropic effect, with a possible effect on axonal conduction dysfunction. Protein synthesis in relation to nerve cell survival, synaptogenesis, neurotransmission and also elaboration of dendritic and axonal processes are affected by steroids. Not to mention it works through NGF-mediated neurite growth. There is also a therapeutic unknown role on damaged neurons, showing responsiveness to exogenous steroids.

Orthognatic surgery often has the risk of peripheral neural damage. A surgery such as a mandibular osteotomy may cause compression by the inferior mandibular nerve due to edema in the tissue around it. There is therefore a tendency of conduction block in the time after surgery. Some surgeries may cause a crush nerve injury where the result is that myelinated axons are reduced. Unmyelinated axons in distal nerves may therefore cause sprouting as late as 12 weeks after surgery.

In 2004 Seo, Tanaka, Terumitsu and Someya published a study on patients undergoing sagittal split ramus osteotomy or intraoral ramus osteotomy. They found that compared to the control group a 4 week treatment with prednisolone initiated 3 or 6 weeks after surgery showed a better recovery than the non-treatment group and treatment initiated after 1 week. The groups receiving treatment after 3 or 6 weeks showed a significant improvement on mechanical touch threshold, and a distinct difference on thermal pain sensitivity,

concluding with prednisolone being an effective drug in facilitating recovery in patients with moderate sensory impairment in the inferior alveolar nerve after surgery. In their paper they call for further research on differential effects and the nerve fiber sensitivity of steroids (64).

Pre-emptive relief

Through recent years several clinical trials have shown the pain relief of glucocorticoids. The effect is usually seen together with the anti-inflammatory effect, both due to reduction of prostaglandins and COX-2 (65). Some trials even conclude that glucocorticoids are insufficient as an analgesic compared to NSAIDs (66). The tissue injury during oral surgery leads to a release of chemical mediators, some affecting hypersensitivity (67). Drugs often target the chemical mediators post-surgically by reducing the already existing amount. The question is; Is it possible by so-called pre-emptive analgesia to prevent or lower this production?

The goal of preemptive analgesia is altering the central changes related to post-operative pain. By administering the drug pre-operatively one hope to affect the CNS plasticity and sensitization, and thereby altering the processing of afferent input (68). With this, the need of post-operative analgesic drugs may be reduced. This subject is however very controversial. In a meta-analysis performed in 2005 the preemptive effect of NSAIDs was statistically significant in 6 out of 12 clinical trials (68). The research on this subject concerning type of drug, amount and time of administration is ongoing.

In a clinical trial at the University of São Paulo the preemptive effect of dexamethasone was compared to the effect of diclofenac following third molar surgery (69). The results showed a statistical significant difference in the mean pain scores of dexamethasone compared to diclofenac and placebo. There was no statistical significant difference in the required rescue medication dosage (69). Although the effectiveness of preemptive analgesia is debated, the meta-analysis from 2005 does not include corticosteroids, and the question is – could this be a valuable future application (68)?

Quality of life after surgery

Corticosteroids are as earlier mentioned used after oral surgery, with effects such as reduced swelling, edema and trismus (70). The question is how the surgery affects the patient in their everyday life. In the recent years measuring the quality of life (QOL) has become more and more common, also in the dental practice. The removal of impacted 3rd molars is an oral procedure very often practiced. This is a procedure often necessitating removal of bone and removal of tissue affecting blood and lymph vessels in connective tissue. The postoperative edema, pain and trismus is then located in an area possibly affecting several other aspects – eating, talking, appearance, sleep and social interactions (70).

In 2011 Majid published a study on 33 patients looking for QOL after removing a mandibular 3rd molar (71). All patients received a questionnaire on day 7, asking for details on speech, sleep, eating, appearance and social isolation. Patients receiving dexamethasone by submucosal injection showed a significant effect on QOL compared to the control group on every score except "speech", and when comparing it to the duration of treatment; on every score but "appearance". This suggests another positive effect of steroid treatment, and a "simple, safe, painless, noninvasive and cost effective therapeutic option for moderate and severe cases" (71).

Neuropathic pain

Recent research has suggested a possible connection between glucocorticoid receptor and the spinal NMDA-receptor (72, 73). Wang and his associates suggested that this interaction is both due to genomic and nongenomic regulation, and that this mechanism may be important in neuropathic pain behavior in rats (72). In their research the central glucocorticoid receptors are found to have an effect on the NMDA receptors after spinal injury. This effect is both on the expression and function (72). Betamethasone is used as a treatment for neuropathic pain today, yet one does not fully know the mechanism (73).

Conclusion

Glucocorticoids have established themselves in general medicine offering excellent treatment alternatives in several pathological conditions. This place in medicine has been earned after years of accumulated clinical experience demonstrating the beneficial effects of the drug, but also showing the adverse effects of the drug. The established place in general medicine and surgery seems to be lacking in dentistry, maybe because of unwarranted fear of adverse effects. Perhaps the time is right for a reassessment of the beneficial values glucocorticoids may offer in dental practice?

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