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PRACTICAL DERMATOLOGY

Corticosteroids and Osteporosis

M García-Bustínduy[a] and MA Gantes[b]

[a]Servicio de Dermatología and [b]Servicio de Reumatología, Hospital Universitario de Canarias, La Laguna, Tenerife, Spain

Abstract. Corticosteroids are the principal cause of secondary osteoporosis due to drug treatment. Doses of more than 5 mg daily and periods of treatment lasting more than 3 months increase the risk of osteoporosis and fragility fractures. It is therefore essential to be aware of measures to reduce the risk of osteoporosis in our patients.

Key words: corticosteroids, osteoporosis, bisphosphonates.

CORTICOIDES Y OSTEOPOROSIS

Resumen. La primera causa de osteoporosis secundaria a fármacos son los glucocorticoides. Dosis diarias superiores a 5 mg o dosificación durante más de 3 meses incrementan la osteoporosis y las fracturas por fragilidad. Resulta crucial conocer las medidas para minimizar la osteoporosis en nuestros enfermos.

Palabras clave: corticosteroides, osteoporosis, bifosfonatos.

Introduction

Corticosteroids have a basic structure composed of 17 carbon atoms in the form of 4 rings, 3 with 6 carbons and 1 with 5. Modifications to this basic structure have made it possible to develop drugs with varying degrees of potency and adverse effects.

The first corticosteroid for medical use, cortisone, was introduced in 1949, although it lacked topical activity. Nevertheless, in 1952, the simple reduction of the carbonyl group at position 11 by Sulzberger and Witten[1] led to the synthesis of what they called compound F, which was later to be known as hydrocortisone, one of the most commonly used topical corticosteroids.[2]

In 1953, introduction of a double bond between carbon atoms 1 and 2 led to the development of prednisone. From 1955 onward, halogenation of 1 of the rings led to a more potent anti-inflammatory effect and paved the way for dexamethasone and betamethasone.

In 1969, a highly penetrative topical corticosteroid 1000 times more potent than hydrocortisone was synthesized—clobetasol.

Correspondence:
Marta García Bustínduy
Servicio de Dermatología, Hospital Universitario de Canarias
Ofra, s/n
38320 La Laguna, Tenerife, Spain
mgarciab@ull.es

Finally, it is worth mentioning the appearance of the systemic corticosteroid deflazacort, an azole derivative that had a lower osteopenia-inducing and mineralocorticoid effect.[3,4]

There are many derivatives and routes of administration, and different esters can often be obtained from 1 product and used in different routes. In the case of some topical corticosteroids it has been possible to maintain anti-inflammatory potency and reduce the capacity for diffusion so that they do not become systemically active. Nonetheless, we must not forget that highly potent topical steroids can be absorbed and that systemic effects associated with their use have been described.[5]

Osteoporosis is a skeletal disorder characterized by a reduction in bone resistance—which is dependent on the density and quality of the bone—that can predispose an individual to fractures.[6] The fundamental cause of the break is the fragility of the bone, not the severity of the trauma.[7] The most common fractures in order of frequency affect the spinal column (they often go unnoticed and are not reported), followed by the distal forearm (Colles fracture), and the proximal femur (patients aged over 75 years).

Bone remodeling is controlled by the so-called basic multicellular units,[8] which can be observed as irregular lacunae on the surface of the trabecular bone or as relatively uniform cylindrical Haversian systems in the cortical bone. The process begins when the osteoblasts covering the bone are stimulated and release factors that bind to osteoclast receptors. This in turn leads to differentiation and activation of these cells, which are responsible for bone resorption.

Subsequently, waves of osteoblasts form the bone matrix. Throughout the remodeling process, a perfect balance between resorption and formation is essential.[6]

Idiopathic osteoporosis is most often associated with old age and the menopause, the latter affecting 35% of women aged over 50 years and 50% of those aged over 75 years.[9]

Chronic corticosteroid therapy is the main cause of drug-related osteoporosis and is known internationally as corticosteroid-induced or glucocorticoid-induced osteoporosis.

Corticosteroids cause osteoporosis by several mechanisms: they reduce levels of sex steroids by inhibition of insulinlike growth factor-1 and corticotropin[10]; they have a direct inhibitory effect on osteoblast receptors that prevents maturation of their precursors[11]; they directly stimulate osteoclastic activity[12] and play an important role in reducing calcium absorption in the small intestine, a function that depends on vitamin D[13]; they also act on kidney cells to reduce renal tubular calcium reabsorption. This increase in renal elimination and the reduction of intestinal calcium absorption lead to secondary hyperparathyroidism, which also contributes to the increase in osteoclastic activity (Table 1).

Densitometry has enabled us to observe losses of 20% in bone mass in the forearm, spinal column, and head of the femur after therapy with corticosteroids.[14]

Most studies have shown that doses greater than 5 mg/d lead to significant bone losses[15] and that, when cumulative doses exceed 30 g, osteoporosis presents in 78% of cases, and the rate of fracture reaches 53%.[16] The levels of bone formation markers such as osteocalcin—a protein synthesized by osteoblasts—and the carboxy-terminal propeptide of type 1 procollagen fall as soon as therapy with these drugs begins and do not recover until 2 weeks after it has been suspended. Furthermore, there is an increase in the urine levels of bone resorption markers such as pyridinoline and deoxypyridinoline.[17] These data point to a very early onset of bone resorption and a marked duration of the effects of corticosteroids on bone metabolism.

Although daily dose, cumulative dose, and patient sex play an important part in the development of osteoporosis, the intensity of the osteoporotic effect of corticosteroids is not the same in all patients taking the same dose, thus implying genetic risk factors for osteoporosis. These may account for up to 75% of the genetic influence in osteoporosis,[18] thereby explaining the extensive variability in the influence of environmental factors such as diet, exercise, and drugs.

Table 1. Routes by Which Corticosteroids Cause Osteoporosis

Reduction of sex steroids by inhibition of corticotropin and IGF-1
Inhibition of osteoblast receptors, with the result that the cells do not mature
Direct stimulation of osteoclasts
Reduced calcium absorption in the small intestine
Reduced renal tubular calcium absorption
Secondary hyperparathyroidism

Abbreviations: IGF-1, insulinlike growth factor-1.

Protocol

The minimum effective dose should be used with any patient who requires therapy with systemic corticosteroids, regardless of the expected duration and recommended dose of treatment. The drug should be administered on alternate days and taken in the morning to respect the circadian rhythm. We can also reduce systemic doses by using topical corticosteroids, not forgetting that these can be absorbed and cause systemic effects.

Clinical History

A clinical history should be taken to confirm individual risk factors (Table 2).

Thus, age greater than 65 years entails a risk of loss of bone mass. Furthermore, women suffer from the disadvantage of a gradual estrogen deficit. Elderly men, on the other hand, have a lower incidence of osteoporosis. Previous fragility fractures indicate that osteoporosis is already established, meaning that additional tests are unnecessary and we can directly consider treatment. A family history of fractures, especially on the mother's side, also points to a greater tendency to suffer from bone fragility. Information on substance use, physical exercise, and daily calcium intake are essential when attempting to correct and prevent osteoporosis. Comorbid conditions such as hyperthyroidism, epilepsy, rheumatoid arthritis, and inflammatory bowel disease, or treatment with heparin should be investigated, as they favor the onset of osteoporosis. The same is true of previous kidney stones, as this can limit treatment with calcium (Table 3).

Additional Tests

A general laboratory workup should be requested for patients expected to undergo long-term therapy (more than 3 months)—eg, those with blistering diseases, connective tissue disease, or severe constitutional eczema. This should evaluate calcium, phosphorous, alkaline phosphatase, 25-

Table 2. Risk Factors for Osteoporosis

Old age
Female sex
Iatrogenic menopause or menopause before 45 years of age
Previous osteoporotic fracture
Substance use Smoking (> 10 cigarettes/d) Excessive alcohol consumption Coffee (> 3 cups/d)
Low calcium intake (< 500 mg/d)
Low exposure to sunlight
Sedentary lifestyle
Prolonged use of corticosteroids
Primary hyperparathyroidism
Rheumatoid arthritis
Hyperthyroidism
Prolonged use of anticonvulsive drugs
Maternal family history of osteoporotic fracture

Table 3. Data to Be Collected in the Clinical History

Age (> 65 years: greater risk of osteoporosis)
Age at onset of menarche and menopause
History of fragility fractures/suspected vertebral fracture (personal and maternal history)
Smoking (number of cigarettes per day, years as a smoker and ex-smoker)
Mean daily intake of calcium (1 glass of milk or 1 yoghurt or 1 portion of cheese = 200 mg of calcium: recommended daily intake, 500-1000 mg)
Habitual physical activity (daily number of hours spent walking)
History of disease: hyperthyroidism, hyperparathyroidism, chronic renal insufficiency, renal lithiasis, inflammatory bowel disease, rheumatoid arthritis, ovarian failure
Drug treatment: corticosteroids (mean daily dose, duration of treatment to date and total cumulative dose to date; thyroid hormone with its daily dose and duration of treatment; anticonvulsives or heparin and days of treatment)
Body mass index (mass, kg/height, m2). An index within the range 18 to 25 is considered healthy.

hydroxyvitamin D, intact parathormone levels, and 24-hour urinary calcium excretion. A simple lateral radiograph of the dorsolumbar spine should be performed, as should bone densitometry at the beginning of therapy.

Treatment

Treatment is advisable for all patients receiving or who are going to receive long-term therapy with corticosteroids. This can be defined as

1. More than 3 months with 5 mg/d or more of prednisone or the equivalent dose of another corticosteroid.

2. More than 4 cycles of corticosteroids during the last year (regardless of the dose).

General Measures

Lifestyle changes should be adopted so that the corticosteroids affect the patient as little as possible (Table 4).

Drugs

Calcium and Vitamin D

Oral vitamin D at a dose of 400 to 800 IU/d and calcium at a dose of 500 to 1000 mg/d should be prescribed to be taken during meals to improve absorption. This supplement is indicated in all patients taking chronic corticosteroid therapy. The dose should be adjusted to the degree of 24-hour urinary calcium excretion detected in the first calcium/phosphorus ratio that will have been requested at the start of the study:

1. Urine calcium less than 150 mg/24 hours: 1000 mg of calcium + 800 IU of vitamin D daily.

2. Urine calcium of between 150 mg/24 hours and 300 mg/24 hours: 500 mg of calcium + 400 IU of vitamin D daily.

3. Urine calcium greater than 300 mg/24 hours. These values indicate hypercalciuria. Instead of calcium and vitamin D, thiazide-type diuretics should be prescribed and the patient should be referred to the osteoporosis and bone metabolic diseases department, generally in the rheumatology service.

A checkup with a calcium/phosphorus ratio should be requested 1 year after starting therapy. If urine calcium is over 300 mg, the checkup should take place every 6 months.

Antiresorptive Drugs

According to the recommendations of the American College of Rheumatology, bisphosphonates have proven efficacious in preventing fragility fractures due to corticosteroid-induced osteoporosis; therefore, they should be recommended to prevent bone loss in all men aged over 65 years, in postmenopausal women expected to take systemic corticosteroids for more than 3 months, and in those patients

Table 4. Lifestyle Recommendations for Patients Taking Systemic Corticosteroids

Give up smoking
Reduce alcohol and caffeine intake
Reduce the amount of salt in diet
Do physical exercise; walk on flat ground for between 30 and 60 minutes every day
Increase dietary calcium intake (1000 mg/d in the form of milk and other dairy products)

whose bone mineral density, calculated by bone densitometry, is under normal limits.[19] Bisphosphonates bind to hydroxyapatite on the surface of the bone and prevent bone resorption.[20]

Risedronate at a dose of 5 mg/d or alendronate at a dose of 10 mg/d can be used. A recent article aimed at dermatologists recommended using risedronate and alendronate in their weekly formulation as they are more easily adhered to.[20] They should be taken under fasting conditions with a glass of water, food should not be taken during the first half hour after administration, and the patient must not lie down for 1 hour after administration so as not to increase the risk of upper digestive tract irritation.

If bisphosphonates are contraindicated (due to difficulty swallowing, reflux esophagitis, or other disorders of gastrointestinal motility), the patient should be referred to the osteoporosis department.

Patients who continue to receive corticosteroids after 1 year should undergo densitometry again to determine changes in bone mineral density.

If the bone mass index has increased, is stable, or has fallen by less than 3% compared with the previous value, we consider the treatment to be efficacious. If bone mass has decreased by more than 3% per year, treatment should be modified.

Finally, if, despite the measures mentioned above, the patient has a pathological fracture, it would be wise to refer him or her to the relevant osteoporosis unit.

Conflict of Interests

The authors declare no conflict of interests.

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