REVIEW ARTICLE

Adverse drug reactions associated with drugs inducing osteoporosis

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ABSTRACT

Drug-induced osteoporosis has a widespread and has a profound impact on the prognosis of patients in chronically serious patients. The most common medicines that cause osteoporotic fractures have been glucocorticoids but in women therapy with aromatase inhibitors, fracture osteoporosis is also identified, Type 2 diabetes mellitus treatment for men and women who are treated with antiandrogen therapy in prostate cancer and women treated with elevated amounts of thyroxine following menopausal procedures. Fracture bone loss also occurs with people who are treated with immune systems drugs such as calcineurin inhibitors, proton-pump inhibitors, heparin, antiretrovirals, loop diuretics, serotonin reuptake selective inhibitors, oral anticoagulants, and anticonvulsants.

KEY WORDS: Drugs; Fractures; Osteoporosis; Secondary Osteoporosis

INTRODUCTION

Adverse drug reactions (ADRs) have been described for as long as medicine has been practiced. In contemporary times, the sudden global elimination of rofecoxib, due to its association with increased risk for cardiovascular use, is significant adverse events, including thalidomide phenomenon,[1-3] and the controversy surrounding selective serotonin reuptake inhibitor and suicide[4] have publicly highlighted the need for pharmacovigilance. These events have attracted much publicity, but it should be recognized that ADRs are a common problem, which affect people in both primary and secondary care every day.

In 1972, the World Health Organization defined ADRs as any reaction to a medication that is dangerous and unexpected and that occurs at doses used in individuals for prophylaxis, diagnosis, or disease treatment or for physiological function alteration.[5]

Bone fragility and increased susceptibility to hip or spine fractures may lead to osteoporosis, a condition marked by low bone density and weakening of the structure of the bone, although any bone may be affected. Men and women of all ages can be affected by osteoporosis, but the risk for elderly women is greater. While in the early stages of osteoporosis, there are no apparent signs, patients can experience height loss, postural changes, or pain secondary to a fracture at later stages. The consequence of osteoporosis is normally a disparity between osteoblast (bone cells) and osteoclastic ones (cells that remove old bone).[6]

Calcium, reduced amounts of estrogen (due to menopause or surgical removal), hyperthyroidism, hypogonadism, and a family history of osteoporosis are correlated with osteoporosis and a lifetime low calcium consumption. Other prominent risk factors include smoking tobacco, overuse of alcohol, Caucasian race, and physical inactivity. However, the fact that such treatments can raise your risk of osteoporosis is perhaps less familiar. This review thus attempts to identify the drugs...
most often linked to osteoporosis, the bone degradation causes and possible alternative drug prescribing to pharmacists to prevent this potentially deteriorating disorder.

**CORTICOSTEROIDS**

Systemic corticosteroid use is the most prevalent indirect source of osteoporosis and the third leading cause. Glucocorticoids are commonly used in various respiratory, pulmonary, gastrointestinal, dermatological, and autoimmune disorders and are efficient. In the first 6–12 months of long-term treatment, the risk of bone deterioration is strongest and seems dose dependence. Many studies have examined the comorbidities of steroid-induced osteoporosis and reported 30–50% fracture in patients with systemic long-term steroids.

Many causes contribute to bone weakening caused by corticosteroids. Glucocorticoids reduce bone development by the apoptosis and lowering bone regeneration rising factors such as osteoprogestins and insulin-like growth factors glucocorticoids decrease. Steroids also improve secondary bone resorption to lower gonadotropin levels (luteinizing hormone [LH], follicle-stimulating hormone [FSH], testosterone, and estrogen). Finally, calcium deficiency caused by steroids has been seen to decrease gastrointestinal accumulation of calcium from the intestines and improve renal calcium excretion. Both these factors play a part in steroid-induced osteoporosis pathophysiology; thus, understanding of complications and bone loss reduction are crucial features of all steroid drug treatment.

Alternatives of long-term treatment are used where possible to prevent the numerous other side effects of corticosteroids, as well as osteoporosis. However, this is not always feasible and corticosteroids may far outweigh the potency of other alternatives in some populations. Where appropriate, steps should be taken in order to use steroids for a brief amount of time, to taper the dose, or to use alternative dosage types including inhalation or topical regimes to avoid systemic complications. Calcium supplements (1200–1500 mg/day) and Vitamin D (400–800 units a day) can be used to avoid bone deterioration, which is particularly necessary for patients with systemic steroids.

Bisphosphonate, as alendronate or risedronate, should be also offered to patients taking chronic steroids. Both pharmaceutical medicines are FDA approved for osteoporosis prevention and treatment. Bisphosphonates impair bone resorption and activity. The same dose is available at either 5 mg once daily or 35 mg once monthly, for the prevention of osteoporosis caused by steroids. It is important to advise patients on doses to avoid gastrointestinal symptoms and to encourage effectiveness for all bisphosphonates. These drugs should be taken with 8 ounces of water on a vacuum, first in the morning. Patients should stay seated or standing for 30 min after taking alendronate or risedronate.

Medicines used for postmenopausal osteoporosis prevention and recovery have not been adequately tested in osteoporosis caused by the medication. Selective estrogen receptor (selective estrogen receptor modulators [SERMs], including raloxifene and calcitonin) and estrogen are included. Estrogen treatment is not effective because of long-term risks, but calcitonin and SERMs could be viable alternatives in specific patients.11

**ANTIEPILEPTIC DRUGS (AEDS)**

Bone damage may be caused by such anticonvulsants. Phenytoin, phenobarbital, carbamazepine, and primidone are the drugs most often associated with osteoporosis. The AEDs are both strong inducers of cytochromes (CYP)-450 isoenzymes. Bone loss almost doubled in women who earned AED relative to their general population in one sample of the elderly community residents.

Several causes for bone loss with AEDs are identified and suggested. All these therapies activate the hepatic CYP-450 enzymes which can lead to a rapid Vitamin D and likely estrogen metabolism as already stated. AEDs are also related to impaired calcium fraction synthesis, secondary hyperparathyroidism, and increased bone turnover. Phenytoin and carbamazepine have immediate effects on the bone at clinical levels, by suppression of osteoblast cells. The inhibition of osteocalcin secretion – a hormone that controls calcium in the bone – is a process which is solely associated with phenytoin. AEDs can have any combination of these effects, and if a mix regime is applied, the impact on bone loss will be additive.

It could be advisable to use a newer AED with a lower frequency of hepatic induction to avoid loss of bone mass associated with conventional AEDs. Long-term experiments still need to be performed to assess if the newer bone agents cause bone damage. Vitamin D and calcium replacement in patients who are stabilized with an older prescription are important for the prevention of bone loss. For those at risk, therapeutic doses are recommended of at least 400 Vitamin D units (IUs) and 1000–1500 mg calcium.

**HEPARIN**

The drug-induced osteoporosis is also associated with non-fractured heparin (unfractionated heparin [UFH]). Usually, this complication is seen in high-dose long-term treatment. Bone loss was estimated to occur after 6 months of heparin treatment at normal doses >15,000 units. Long-term UFHs are not as frequent as they have been administered for newer low-molecular-weight heparins (LMWHs). The LMWHs are reliable, need less surveillance, and are easily implemented in an ambulatory environment. In one research, the use of enoxaparin did not lead to major improvements in the density...
of bone minerals in women treated during pregnancy and 6 weeks after childbirth.

It is not well known the precise cellular mechanism by which heparin contributes to bone loss. Heparin induces increased osteoclastic resorption and the suppression of osteoblast function which leads to a reduction in bone mass. Other pathways suggested include mast cell loss in the bone marrow and improvement of the role of parathyroid hormone (PTH), an important calcium regulator in the body. The PTH effects enhance the release of calcium and phosphorus into the blood to elevate serum levels. In addition to low serum calcium, PTH is typically released.

PROGESTINS

Progestins are one of the new groups of osteoporosis-related drugs. Progestins are a type of hormone common in different types of contraceptives and are, therefore, used for hormone replacement products in women of a diverse age. Medroxyprogesterone acetate (MPA) is the most common progestin preparation associated with bone loss (MPA). It is known as Depo-Provera as an injectable form of birth control which also contains hormone substitution variations known as Premphase and Prempro. After 2 years of consistent use of MPA, the chance of bone damage increases. Since Depo-Provera is widely used in teenage girls, new interest has arisen in this demographic for osteoporosis prevention through the encouragement of calcium supplement and the restriction of length. In adolescents, where there are no other alternatives, MPA should be used for up to 2 years. However, other means of birth control, such as oral combination pills, may be advisable if long-term contraception is required.

The bone loss effects of medroxyprogesterone depend on the patient’s dosage and estrogens. MPA eliminates ovarian estrogen development. Estrogen protects against bone degradation and as already noted, low estrogen levels can cause bone mass to deteriorate. MPA also prevents the secretion of LH and FSH by gonadotropin. MPA also displays corticoid properties and can lower the differentiation of osteoblast by occupying the glucocorticoid receptor. During osteoporosis, MPA can have a beneficial impact on bone density, however, some progestins including nortestosterone and norethindrone.

OTHER MEDICATIONS

The aforementioned medicines bear the greatest documented risk of osteoporosis, but other medicines are also associated with bone damage. When used at extremely high doses, such as oncology patients, methotrexate can increase the risk of osteoporosis. The mechanism is not well known, however requires a bone resorption and forming mismatch. Diuretic loops (for example, furosemide) can also lower bone mass by increasing the excretion of calcium within the kidney. Excess thyroid supplementation is another possible source of bone loss. The result is demineralization of the bone. This typically happens only where the thyroid-stimulating hormone content is nearly undetectable due to an over supplement. Antacids containing aluminum can bind calcium to the gastrointestinal tract and result in a decreased absorption of calcium. Lithium has demonstrated that it is more secretive with PTH, which can induce calcium from the bone to increase serum calcium levels, as shown above. There have been elevated bone turnover and losses of cyclosporine and tacrolimus in some animal models. Warfarin and Vitamin K deficiency causing compromised bone production are also a disputed argument. While osteoporosis has been associated with these drugs, the evidence is not as conclusive as the available literature on corticoids, AEDs, heparin, and progestin.

PREVENTION AND TREATMENT

Osteoporosis identification along with risk factors has become significant public health issues for its growth, prevention, and care. Awareness of drugs that may contribute to bone deterioration in all populations of patients is critical for preventing long-term problems that may only occur later in life. It is also necessary in teens and in the whole of life to increase bone weight.

A proper intake of calcium and Vitamin D from a diet, exogenous addition, or both is the first step in prevention. For teenagers (ages 9–18), calcium requirements are highest; the recommended age group is 1.300 mg/day. The maximum calcium consumption is 1.000 mg daily between the ages of 19 and 50. The suggested consumption is 1.200–1.500 mg/day for patients over 50. The highest dose that can be taken by the body, if an extension is taken, should not be more than 500 mg at a single time during the day. Dose division can be broken up into 2 or 3 times a day. Exposure to sunshine, diet, or exogenous supplementation can satisfy Vitamin D requirements. Experts propose a daily consumption of 400–800 IUs. And with doctors, permission doses >800 IU/day of Vitamin D should be prescribed. Lower Vitamin D doses may be needed for patients with renal dysfunction.

IMPLICATIONS FOR PHARMACY PRACTICE

Drug-induced osteoporosis is currently underdiagnosed but is a potentially preventable disease. Osteoporosis affects a large patient population, with billions of dollars’ worth of health-care costs. The identification and tracking of suspected opioid causes and the use of preventive intervention will greatly enhance patients’ quality of life. A diet high in calcium and Vitamin D should be promoted by pharmacists who consider patients at risk for bone loss. It must prohibit smoking, heavy intake of alcohol, and caffeine. Special dietary advice may be given to refer patients to a...
licensed dietitian. Pharmacists may also provide over-the-counter supports such as transdermal nicotine for smoking cessation therapy. Another important suggestion is to note the calcium-retaining properties of thiazide diuretics which will shield you from the disease. As first-line medications for hypertension treatment, thiazides should be prescribed in particular for patients with osteoporosis risk factors. Normal weight-bearing and patient prescription enforcement should be supported by pharmacists.

Pharmacists may suggest to call the prescribing doctors to recommend corrective measures when at-risk patients are detected. Corticosteroid treatment options can be difficult to assess and not recommended. It must be recalled, though the utilization of systemic corticosteroids raises the likelihood of osteoporosis undeniably. Pharmacists can also advise doctors and patients to become conscious that using Depo-Provera will raise the likelihood of bone mineral degradation for longer than 2 consecutive years. The treatment of osteoporosis associated with drugs other than AIs is lacking in detail.

CONCLUSION

Pharmacists can play an important role in identifying and avoiding associated fractures the risk for drug-related osteoporosis. Since osteoporotic fractures have morbidity and mortality, steps to mitigate this risk can have serious health consequences. A thorough understanding of drug caused osteoporosis is required for pharmacists and patients seeking care must be established. Fracture avoidance is the ultimate goal of counseling which calls for good cooperation between patients and other health providers.

REFERENCES


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