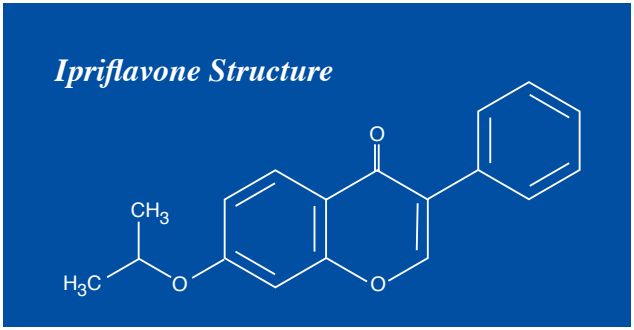

Ipriflavone

Introduction

Ipriflavone (IP), chemical structure 7-isopropoxy-isoflavone, is an isoflavone, synthesized from the soy isoflavone, daidzein. Ipriflavone was discovered in the 1930s but has only recently begun to be embraced by the medical community in this country. Over 150 studies on safety and effectiveness, both animal and human, have been conducted in Italy, Hungary, and Japan. As of 1997, 2,769 patients had been treated and studied, for a total of 3,132 patient years.[1] From the weight of the evidence, ipriflavone holds great promise in the prevention and treatment of osteoporosis and other metabolic bone diseases.

Pharmacokinetics

Ipriflavone is metabolized mainly in the liver and excreted in the urine. Food appears to enhance its absorption. When given to healthy male volunteers, 80 percent of a 200-mg dose of ipriflavone was absorbed when taken after breakfast.[2] Ipriflavone metabolism was not found to be significantly different in elderly osteoporotic or mild kidney failure patients than in younger, healthy subjects.[3] Studies using labeled IP in rats found it concentrated primarily in the gastrointestinal tract, liver, kidneys, bones, and adrenal glands.[3]

Mechanisms of Action

Anti-resorptive Mechanisms

An animal study found ipriflavone inhibited parathyroid hormone-, vitamin D-, PGE2-, and interleukin 1β-stimulated bone resorption.[4] Bonnuci et al found parathyroid-stimulated osteoclastic activity and resulting hypercalcemia were inhibited in a dose-dependent manner by ipriflavone supplementation in rats.[5]

Bone-forming Mechanisms

An *in vitro* examination of the osteoblastic effect of ipriflavone and its metabolites resulted in interesting findings. Ipriflavone and one of its metabolites stimulated cell proliferation of an osteoblast-like cell line (UMR-106a – a cell line often used to determine the effect of various hormones and drugs on bone metabolism). IP and another metabolite increased alkaline phosphatase activity, while another metabolite enhanced collagen formation; IP alone inhibited parathyroid hormone activity.[6]

Lack of Direct Estrogen Effect

One of the benefits of ipriflavone in the treatment of osteoporosis is its lack of direct estrogenic effect. Melis et al administered ipriflavone or placebo to a group of 15 postmenopausal women. LH, FSH, prolactin, and estradiol were measured after a single oral dose of 600 or 1,000 mg, and after 7, 14, and 21 days of treatment with 600 or 1,000 mg doses. No differences in endocrine effect were noted between the ipriflavone and placebo groups. Vaginal cytology was unchanged after 21 days of IP or placebo compared to a significant increase in superficial vaginal cells in the estrogen group.[7]

In vitro investigation of the interaction between ipriflavone and preosteoclastic cell lines found it was not mediated by direct interaction with estrogen receptors.[8] Instead, unique binding cites for ipriflavone were identified in the nucleus of preosteoclastic cells. The presence of IP binding sites was confirmed by Miyauchi et al. They identified two classes of binding sites in chicken osteoclasts and their precursors.[9] Similar ipriflavone binding sites have been identified in human leukemic cells, a line with similar characteristics to osteoclast precursors.

Calcitonin secretion is modulated by estrogen and, while ipriflavone alone did not enhance calcitonin levels, it acted synergistically with estrogen, necessitating lower doses of estrogen to achieve normal calcitonin secretion. It appears IP increases the sensitivity of the thyroid gland to estrogen-stimulated calcitonin secretion.[10]

Clinical Indications

In the last decade there have been over 60 human studies – many double blind and placebo controlled – on the use of ipriflavone for the prevention and reversal of bone loss. An overview of these studies follows.

Postmenopausal Osteoporosis

Ipriflavone has been studied in numerous double-blind, placebo-controlled trials conducted in Italy, Hungary, and Japan. The same protocol was used throughout most of the studies – 200 mg ipriflavone or placebo three times daily. In most of the studies, calcium (500-1000 mg) was given to both ipriflavone and placebo groups. Several two-year studies looked at women immediately postmenopause (age 50-65) and found bone mass was maintained or improved slightly in the ipriflavone groups while those in the placebo groups experienced significant bone loss.[11-14]

It appears ipriflavone may be particularly effective for the treatment of so-called "senile osteoporosis" (osteoporosis in women or men over the age of 65) as evidenced by the results of two studies in seven Italian centers.[1,15] In these studies a total of 112 subjects aged 65-79 were followed for two years. Subjects took either 600 mg ipriflavone plus 1 g calcium daily or placebo plus 1 g calcium. A four- to six-percent increase in bone density was observed in the ipriflavone groups, whereas the placebo groups experienced as much as a three-percent

decrease in bone density. The most clinically relevant finding in the larger of the two studies was a decrease in fracture rates in the IP group (2 of 41 patients experienced fractures in the IP group, whereas 11 of 43 experienced fractures in the placebo group).[1]

A recent four-year study published in *JAMA* found no significant change in bone mineral density in a group of postmenopausal osteoporotic women taking ipriflavone (n=234) at a dose of 200 mg three times daily when compared to placebo (n=240). While bone density did not increase significantly, neither was significant loss reported in either group. Unlike previous studies, this study did not divide the treatment groups according to age but combined all ages (45-75 years).[16]

Ipriflavone for Osteoporosis in Combination with Other Nutrients or Medications

Ipriflavone has been found to enhance the effect of other bone-preserving agents, including 1α vitamin D (a form commonly used in Japan for osteoporosis).[17]

A number of studies have examined the effect of ipriflavone and estrogen for the treatment of osteoporosis. While low doses of conjugated estrogen (0.15-0.30 mg/day) typically are high enough to prevent hot flashes and other neurovegetative symptoms of menopause, a somewhat higher dose (0.625 mg/day or higher) is generally necessary for bone protection. Some studies, however, have found that when combining ipriflavone and estrogen, lower doses of estrogen afford protection.[18-20]

Ipriflavone versus Salmon Calcitonin

An open, controlled 12-month trial compared ipriflavone with salmon calcitonin in 40 postmenopausal women. Significant increases in bone density were observed in both groups after 12 months: a 4.3 percent increase in BMD in the ipriflavone group and a 1.9-percent increase in the calcitonin group.[21]

Ipriflavone in the Prevention of Surgical or Drug-induced Osteoporosis

Researchers examined the effect of ipriflavone in restraining bone loss induced by gonadotropin hormone-releasing hormone agonists (GnRH-A) such as Lupron®, used to induce ovarian atrophy for the treatment of endometriosis, uterine fibroids, etc. In a double-blind, placebo-controlled trial 78 women treated with GnRH-A (3.75 mg leuproreline every 30 days for six months) were randomly assigned to receive either ipriflavone (600 mg/day) or placebo; both groups received 500 mg calcium daily. In placebo subjects, markers of bone turnover (urinary hydroxyproline and plasma bone Gla) were significantly elevated while BMD decreased significantly after six months. Conversely, there were no changes in BMD or bone markers in the ipriflavone-treated group.[22]

Animal studies have found ipriflavone inhibited bone loss associated with long-term steroid use[23] and immobilization.[24,25]

Other Conditions

Several other pathological conditions involving bone may be helped by ipriflavone, including Paget's disease of the bone,[26] hyperparathyroidism,[27] otosclerosis,[28] and renal osteodystrophy.[29]

Drug-Nutrient Interactions

A reduction in theophylline metabolism and increased serum theophylline was observed in a patient being treated with ipriflavone.[30] Animal studies have indicated this may be due to inhibition of certain cytochrome p450 enzymes, resulting in diminished elimination of the drug via the liver.[31,32] While ipriflavone does not have a directly estrogenic effect, it appears to act synergistically with estrogen to normalize calcitonin levels.[10]

Side Effects and Toxicity

In general, ipriflavone appears to be quite safe and well tolerated. As of 1997, long-term safety of ipriflavone (for periods ranging from 6-96 months) had been assessed in 2,769 patients for a total of 3,132 patient years in 60 human studies.[1] The incidence of adverse reactions in the ipriflavone-treated patients was 14.5 percent, while the incidence in the placebo groups was 16.1 percent. Side effects were mainly gastrointestinal (GI). Since the placebo groups in most studies received calcium, it is not unreasonable to assume calcium may have as much to do with GI effects as ipriflavone. Other symptoms observed to a lesser extent include skin rashes, headaches, depression, drowsiness, and tachycardia. Minor transient abnormalities in liver, kidney, and hematological parameters were documented in a small percent of subjects. One study found subclinical lymphocytopenia as a side effect of treatment in 29 of 474 postmenopausal participants.[16] Why this effect on white blood cell count had not been found in previous studies is unclear; however, it might be prudent to conduct periodic CBCs on patients using long-term ipriflavone therapy.

Dosage

Dosage for treatment of osteoporosis has been consistent – 200 mg three times daily. The most successful dosage for Paget's disease was 1,200 mg daily for 30 days, followed by 600 mg daily.[26] Hyperparathyroidism was treated with 1,200 mg daily,[27] otosclerosis with doses of 200 mg four times daily,[28] and renal osteodystrophy with doses of 400-600 mg daily.[29]

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