Ipriflavone

Osteoporosis Education Project Analysis

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Flavonoids

Flavonoids are a large group of compounds found in plants. As plant pigments they are largely responsible for the colors of many fruits, vegetables, herbs and flowers. Plant flavonoids have many valuable properties and are often antioxidants, anti-inflammatory, anti-allergy, and anticarcinogens. Over 4,000 flavonoid compounds have been identified and classified according to their molecular structure. Within the large category of flavonoids there are numerous substances classified as "isoflavones". These isoflavones are often called "phytoestrogens", or "plant estrogens" because of their structural similarity to human estrogen. To varying degrees the isoflavones can mimic some of the effects of human estrogen.

Ipriflavone History and Background

Ipriflavone falls into the large group of isoflavonoids. Ipriflavone as used today as a bone building agent is a synthetic isoflavone derivative. It was first synthesized in Hungary by Doctor Laszlo Feuer while researching flavonoids as essential growth factors in animals. Soon after its synthesis ipriflavone was used in clinical testing. The substance was reportedly first used in veterinarian fodder and experimented with as an agent for enhancing endurance in animals. It was also investigated as a potential anti-anginal agent and was seen to influence the mitochrondrial energetics in a positive manner, with an oxygen sparing effect.

Early on it was seen that ipriflavone administration led to increases in the skeletal calcium of sheep, rats and chickens. Through the 1970's experiments were conducted using ipriflavone to enhance bone health in animals. This preliminary work was followed by dozens of clinical studies in Hungary, Japan and Italy using ipriflavone with humans.

Ipriflavone is registered as a prescription treatment for osteoporosis in various countries including Japan and Argentina. Ipriflavone has been shown to increase bone calcium retention, inhibit bone breakdown, promote activity of the bone-building cells, and reduce the pain of osteoporotic fractures. Despite the fact that in structure it is similar to phytoestrogens like genistein and daidzein, ipriflavone has not been shown to exhibit estrogenic activity on the classic estrogen target organs. Thus it has not been reported to have the deleterious side-effects on breast and uterine tissue of estrogen therapy.

Efficacy of Ipriflavone For Halting Bone Loss and Reducing Fractures

Numerous studies document a halting of bone loss and increases in bone density with the daily use of 600 mg ipriflavone. Between 1989 and April, 2000 there were reported in the English language some 31 human clinical studies on ipriflavone. These studies involved a total of 4298 patients. Of these, 1495 patients were treated with ipriflavone. Of the 31 studies, 18 were placebo-controlled looking at bone mineral density. Of these 18, about one half showed ipriflavone to either enhance bone density or reduce bone loss significantly more than calcium alone. Although no early studies had fracture as their end point, three Italian studies strongly suggested that ipriflavone reduced vertebral fractures.

In an attempt to define further the efficacy and safety of ipriflavone, a multi-centered three year European trail on ipriflavone was organized (IMEFS). In October, 2000 a summary of the research findings of this study was presented at the American Society of Bone Mineral Research in Toronto. At this meeting Dr. Alexandersen from Denmark reported that this trial, in contrast to most other studies, did not find ipriflavone use associated with an increase in bone mineral density. That is, women on just calcium did as well as women on ipriflavone and calcium. (We suspect the failure of ipriflavone to improve bone mineral density more than calcium was because study women were not undergoing current bone loss). A second finding of the European study was ipriflavone did not significantly reduce fractures in this three year study. The authors reported, however, that the study was "underpowered" that is, too small to really test for the reduction in fracture.

Safety Concerns

The European IMEFS differed from dozens of other studies also by highlighting a safety issue. This European study reported, that ipriflavone use caused an overall slight average decrease in lymphocytes (a subtype of white blood immune cell); and caused an excessive decrease in lymphocytes (lymphopenia) in 29 of the total 234 women on ipriflavone. On the other hand, only one women in the control group was reported to develop such lymphopenia. The 29 women with lymphocytes lowered into the danger zone were withdrawn from the study. The women with lowered lymphocyte counts, they reported, had no symptoms of immune suppression and most, if not all, reportedly recovered baseline lymphocyte counts after discontinuing ipriflavone. Neither the mechanisms by which ipriflavone lowered the lymphocyte count, nor the long term implications of this action were know to the researchers. Reportely, such changes in lymphocyte count generally occurred within the first year of ipriflavone use. While the data sets from this study have not been made public, a bit further down you will find a summary of the IMEFS report as we best understand it. Also below you will find our suggested guidelines for ipriflavone use.

A second safety issue with ipriflavone use concerns its ability to inhibit selected liver cytochrome P450 detoxification enzymes, much like the action of the flavonoids in grapefruit juice. This means that the body’s detoxification or inactivation of certain drugs and chemicals which depend on selected P450 cytochrome pathways could potentially be

altered in those using ipriflavone. From its many years of use, however, we can only find three reported cases of such interaction. There have been reported three cases where blood medication levels became high in association with ipriflavone use. Two cases involved concomitant use of ipriflavone and Coumadin (S-warfarin) while the other involved high levels of theophylline in a very compromised individual also using ipriflavone. As you will note in the Italian guidelines given below, patients using Coumadin should be monitored for clotting parameters and treated with careful medical supervision should they use ipriflavone. More information on this topic can be found in the articles by Monostory et al., the abstracts of which are in the Ipriflavone Bibliography With Abstracts.

By far the most common side effect of ipriflavone concerns digestive complaints and, as explained in the Italian guidelines, those hypersensitive to the product, or those with active gastric or duodenal ulcers should not use ipriflavone. Some sensitive individuals appear to develop diarrhea with ipriflavone requiring cessation of the substance.

Summary of Ipriflavone Multicenter European Fracture Study (IMEFS)

Overall Design

- The study was a randomized trial with 474 women in total.
- 234 women assigned to take Ipriflavone (200 mg three times a day for a total of 600 mg) plus Calcium (500 mg).
- 240 were assigned placebo; plus Calcium (500 mg).
- Subjects were osteoporotic women, aged 63+/- 6 years, with a natural menopause at least 1 year before entering the study.
- The women had low bone mass (vertebral BMD corresponding to at least 2 standard deviations below the premenopausal mean value) and no prevalent vertebral fractures.
- The study was multi-centered (Belgium, Denmark and Italy) and of three years duration.

Findings on Bone Mineral Density Oct. 2000:

No statistically significant difference in annual percentage change from baseline lumbar spine and bone mineral density was reported between those given ipriflavone and those given calcium. The only published information of this study is an abstract by Dr. Alexandersen which is included in the Ipriflavone Bibliography With Abstracts.

Comment on Statistical Analysis

Although the researchers sparingly reported the statistics and "P values" of the data (used to assess if a result is statistically significant but not necessarily clinically meaningful) they did not provide full data on the confidence intervals. From the limited data presented, it is not possible to detect what percentage of women using ipriflavone benefited from the therapy.

Safety Aspects Reported in Study

As a group, IP treated patients were reported to show an overall reduction in lymphocytes (from 33% to 27%) (Note: The normal range of lymphocytes is 20% to 40% of the total white blood cells). Twenty-nine patients, however, developed an excessive lowering of lymphocytes (lymphopenia) and were withdrawn from the study. There were no clinical manifestations of immune weakness (infections, etc.) noted in any of the patients who developed lymphopenia, as reported by IMEFS researchers.

Aside from the lymphocytes changes, the total number of Adverse Event Reports (AER) were nearly identical for placebo and ipriflavone patients.

Summary of Lymphocytes Changes Noted in Previous Studies

Of all the published English language ipriflavone studies prior to the IMEFS study, two give specific numbers regarding lymphocyte reductions. The most complete statistic was reported in 1997 by Agnusdei and Buffalino in which they reported that 2.96% of patients tested (22 of 749) exhibited out-of-range (low) lymphocyte counts.

Current Better Bones Better Body Perspective for Ipriflavone Users

1. The Better Bones, Better Body Program seeks the maintenance and regeneration of bone health through natural, life-supporting means that are good for bone and good for the entire body. When such natural nutrition, exercise, lifestyle and attitudinal modifications fail to reduce high bone turnover, halt bone loss and reduce osteoporotic fractures, stronger therapies may be required. Ipriflavone is one of these stronger agents, along with a host of prescription drugs marketed for osteoporosis. The Better Bones Better Body Perspective views ipriflavone as an alternative to drug therapy to be used only when a nutritional, exercise, lifestyle and attitudinal programs is ineffective.

2. Our own year long small pilot study confirmed what dozens of other larger studies have reported. That is, ipriflavone is generally effective at halting bone loss in postmenopausal women who are undergoing excessive bone loss. In our study the women had been losing bone for several years, even in the face of good nutritional supplementation with calcium and other nutrients. With ipriflavone most were able to halt the loss and at times begin building bone. Ipriflavone, on the other hand, may well not do very much for those who are not actively losing bone, even though they may have osteoporosis, as suggested by the new European IMEFS study.

3. Ipriflavone has been used in Italy, Japan and many other countries for years and reported as both effective and safe. Yet, there appears to be some safety concerns. The major concern involves the finding that ipriflavone might lower the white blood cells known as lymphocytes in some individuals. Earlier Italian studies mentioned occasional drops in WBC, and the Italian guidelines for ipriflavone use printed below suggest monitoring lymphocytes. The European IMEFS study reported a much higher incidence of significant lymphocyte drops when using ipriflavone than did any other study. Obviously this conflict in the data should be resolved by careful analysis of the data and new studies as necessary. We have not been able to obtain the raw data sets from this European IMEFS study, although several requests have been made to the drug company that owns the data.

4. As discussed in the below listed Italian Chiesi Pharmacy guidelines for ipriflavone use, some people can experience digestive problems from ipriflavone. Those with active gastric or duodenal ulcers should not use ipriflavone nor should those who experience diarrhea or gastric distress with its use. Also, ipriflavone can interact with the liver detoxification of certain drugs like the anti-clotting medication Coumadin or possibly with theophylline detoxification. Ipriflavone should not be used with these medications unless under careful medical supervision.

The Bottom-line For Ipriflavone Users

Until the data becomes totally clear, which will likely require North American studies, it is wise to use ipriflavone under appropriate medical supervision. Have your health professional check your white blood cell count and lymphocyte count before using ipriflavone and then at six months, a year and every year thereafter. Most changes reportedly occur within the first six months or one year, but a yearly check up is wise. Anyone who develops excessively low lymphocytes should go off ipriflavone. Also, if you are on other mediations, have kidney, liver or other serious health problems ask your physician to decide on the suitability of ipriflavone. In addition, as with any bone-building program, you want to check for normalization of bone breakdown markers (such as the NTx Osteomark) and for stabilization or improvement in your bone mineral density. Any program that does not reduce high bone resorption markers within one year, or halt bone loss within two years, should be modified.

Also note: This above information on ipriflavone represents our best summary of the research findings and is provided for educational purposes only. This information in no way stands for, or substitutes for, medical advice from a qualified health professional.

Italian Guidelines for the Use of Ipriflavone

For many years ipriflavone has been used as a prescription medication for the treatment of osteoporosis and low bone density in Italy. It is known as "Osteofix 200" in Italy. It is produced and marketed by the Chiesi Pharmacy. Below you will find the guidelines and pharmaceutical property sheet for ipriflavone use as developed and distributed by the Chiesi Pharmacy, Parma, Italy.

OSTEOFIX 200

QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains:
active principle: ipriflavone 200mg

PHARMACEUTIC FORM

Simple tablets for oral use

CLINICAL INFORMATION

Therapeutic Directions:
Post-menopausal and senile osteoporosis.

Dose and way of administration:
One 200mg tablet three times a day, after the main meals.

Contraindications:
Hypersensitivity to the drug. Gastric or duodenal ulcer in active phase.
Lymphocytopenia. The product is contraindicated during infancy and in pregnant or presumed pregnant women.

Special instructions and use precautions:
Administer the drug with special caution to patients with severe liver or kidney damage and hematological troubles. In case of long term treatment, it is suggested to control periodically the parameters of liver and kidney functionality and the hematologic parameters (red cells count, absolute and differential white cells count). If the values are altered, it is suggested to interrupt the treatment and perform periodical checks until the parameters return normal.

There is no information about the safety of the product in the infancy.

Keep the drug out of the reach of children.

Interactions:
If administered to patients under cumarinic anticlotting therapy, ipriflavone determines an increase of its activity; hence, it is suggested to monitor clotting parameters and, if necessary, to adjust the dose of the anticlotting drug. No interactions have been observed with oral hypoglycaemic drugs (sulfaniluree) in diabetic patients.

Pregnancy and breastfeeding:
Ipriflavone is able to pass through the placental barrier, therefore, it is precautionary to not administer the drug during pregnancy or presumed pregnancy.

The drug is to be administered with caution to breastfeeding women, since its passage into the mother's milk has been shown in animal studies.

Effects on driving and machinery use skills:
Not known

Side effects:
While treated with ipriflavone, the patient can show occasional hypersensitivity reactions (skin rashes, itch), gastrointestinal troubles (nausea, vomiting, gastralgia, diarrhea), dizziness. Occasionally increases in SGOT, SGPT and bilirubinemia can be observed: increases in azotaemia, reduction in red and white cells. Granulocytopenia and lymphocytopenya have been observed very rarely, and went back to normal after interruption of the treatment.

Overdose:
There are no known cases of overdose with ipriflavone. In case an overdose should occur, we suggest to perform a gastric washout and treat symptomatically.

PHARMACEUTCAL

Pharmacodynamic properties:
Osteofix 200 contains ipriflavone, an isoflavonic derivative which, as demonstrated on different experimental models of osteoporosis, is able to inhibit the loss of bone mass (osteolysis) and to favor both differentiation and stimulation of osteoblasts with subsequent deposition of new bone tissue (osteogenesis) through direct mechanisms.

Moreover, ipriflavone is able to potentiate the effects of endogenic estrogens on the bone metabolism.

It has also been shown, both in experimental models and in clinical studies on women in menopause, the absence of direct estrogenic effects.

In vitro, ipriflavone reduces the release of labeled calcium from fetal rat bone calcium cultures. This effect is notable also in the presence of the stimulant action on the calcium release by the parathyroid hormone or the prostaglandin PGE2. In vivo, ipriflavone reduces significantly the bone reabsorption induced by transplant of parathyroid in rats.

In experimental osteopathy derived from diet lacking in calcium and vitamin D in rats, ipriflavone has a positive effect on the density and the weight of the bone structure and on the calcium content. In the osteoporosis determined by glucocorticoids in rat, administration of ipriflavone determines, compared to controls, an increase of the density of distal metaphysis and tends to increase the density of femoral diaphysis.

In the newborn rat, ipriflavone inhibits the bone demineralization caused by calcitriola. In the diabetes due to streptozotocyn, ipriflavone inhibits the reduction of bone density and of bone calcium and phosphates content, without influencing the diabetic condition.

In clinical applications, ipriflavone has been effective in the prevention and in the treatment of post-menopausal and senile osteoporosis: the characteristic symptoms of the disease (pain while resting, while walking, while performing rotational and bending movements) regress within the first weeks of therapy; the parameters expressing the state of the bone mass improve and stabilize after the first weeks of treatment (the bone density increases or stops to decrease, the number of vertebral collapses and fractures due to compression and the number of spontaneous or traumatic fractures of the long bones decreases). The antiosteoporosis activity and the tolerance to ipriflavone remain constant during long term treatments.

Pharmacokinetic properties:
If orally administered to humans, ipriflavone is rapidly absorbed and metabolized. The main plasmatic and urinary metabolites are three; they are partly responsible for the activity of this product.

It has been observed that the absorption of the drug is higher if taken when the stomach is full, after the main meals. No accumulation has been observed in cases of long term treatment.

Preclinic security data:
Ipriflavone has little acute toxicity and is well tolerated in long term treatments. The LD50 values for oral administration are higher than 10,000 mg/kg in mouse and rat, and 3,500 mg/kg in the dog. In treatments prolonged for a year no sign of intolerance or anomalies have been observed for doses up to 3,000 mg/kg/day in the rat and up to 1,500 mg/kg/day in the dog. Ipriflavone did not influence significantly rat fertility up to 3,000 mg/kg/day, nor produce teratogenic or embriotoxic effects on rat or rabbit up to 3,000 mg/kg/day, nor negative effects on pre- and post-natal development of rat puppies up to 1,000 mg/kg/day.

No mutagenic effects have been observed on numerous experimental models in vitro of procaryotes and eucaryotes, nor on human cells genoma, nor carcinogenic potential on mice treated for 18 months with doses up to approximately 300 mg/kg/day, and in rats treated for 24 months with doses up to approximately 240 mg/kg/day.

PHARMACEUTIC INFORMATION

Excipients:
Microcristallin cellulose, crospovidone, polivinilpyrrolidon, modified starch, magnesium stearate, precipitated silicium, sodium laurilsulphate.

Incompatibility:
None.

Validity:
5 years.

The indicated period of validity refers to the sealed package, correctly preserved.

Special precautions for conservation:
The product has to be kept at normal environmental conditions.

Container, package and price:
Internal package: bister in PVC/A1 thermally formed and thermally welded.

External package: box in printed thin pasteboard.

Box of 30 tablets of 200 mg &endash; Price 47,000 Lit.

Use instructions:
See paragraphs "Dose and way of administration" and "Special instructions and use precautions".

AUTHORIZATION NUMBER

AIC n. 027493016

DATE OF FIRST AUTHORIZATION OR RENEWAL

March 1, 1990

TABLE ACCORDING TO DPR 309/90

N/A

SALE INSTRUCTIONS

To be sold under refillable medical prescription

DATE OF TEXT REVISION

April 1997

OWNER

CHIESI FARMACEUTICI S.p.A.

Via Palermo 26/A

43100 – PARMA

Susan E. Brown, Ph.D.,CCN

A medical anthropologist and certified nutritionist, Dr. Susan E. Brown has consulted widely on socioeconomic, cultural, educational and health issues. She has taught in North and South American universities and authored numerous academic and popular articles.

Currently, Dr. Brown directs the **Osteoporosis Education Project** and the **Nutrition Education and Consulting Service** in Syracuse, NY. With the **Osteoporosis Education Project** she conducts primary research, lectures widely on osteoporosis prevention and reversal, and teaches the use of a holistic, natural program for the regeneration of bone health. The **Nutrition Education and Consulting Service (NECS)** provides consulting, education, research and lecture services for health professionals and the public. In addition to running a busy private practice, Dr. Brown serves as a consultant to various medical and industry groups.

Further information on Dr. Brown, her publications and her work, is available on the attached biography or at www.betterbones.com and www.susanbrownphd.com

The Osteoporosis Education Project

The Osteoporosis Education Project (OEP) is a non-profit, public interest research and education organization located in Syracuse, NY. Its mission is to explore the human potential for bone health maintenance and regeneration, seeking natural ways to build and rebuild bone. As a part of our public interest work OEP studies and attempts to document the efficacy of natural bone building products and formulations. Information on OEP research and education efforts can be found on their website www.betterbones.com

As the Director of The Osteoporosis Education Project I have had the opportunity to experiment widely with natural bone-building programs. Unfortunately, I have learned that it is often difficult to halt bone loss, much less rebuild bone, with simple natural means. Given our experience, we are constantly looking for new natural formulations, which report success in halting and even beginning to reverse osteoporosis.