SOUTHWESTERN NEWS

Contact: Jennifer Donovan
(214) 648-3404

**SLOW-RELEASE FLUORIDE IS SAFE,
EFFECTIVE OSTEOPOROSIS TREATMENT**

DALLAS — September 15, 1995 — Slow-release fluoride supplemented with calcium citrate builds normally mineralized, apparently stronger bone and prevents new spinal fractures in postmenopausal women with osteoporosis, researchers from UT Southwestern Medical Center at Dallas report in today's issue of *Annals of Internal Medicine*. The journal article presents final results of a randomized clinical trial of a slow-release form of sodium fluoride with calcium citrate supplementation.

Dr. Charles Y.C. Pak and his colleagues also presented their findings on slow-release fluoride at the annual meeting of the American Society for Bone and Mineral Research in Baltimore this week. They gave two presentations, one on the randomized trial and another confirming randomized results by findings in two larger, nonrandomized trials conducted at UT Southwestern and nine other medical centers.

"Intermittent slow-release sodium fluoride supplemented with calcium citrate builds in the spine what appears to be structurally normal, mechanically improved bone, produces a sustained increase in spinal bone mass, inhibits spinal fractures without increasing hip or other fractures and reduces back pain in postmenopausal women with established osteoporosis who have already sustained fractures," Pak said. "And it does this without harmful side effects."

Director of the Robert T. Hayes Center for Mineral Metabolism Research at UT Southwestern, Pak holds the Distinguished Chair in Mineral Metabolism and is the Donald W. Seldin Professor in Clinical Investigation.

A new drug application for slow-release sodium fluoride for the treatment of postmenopausal osteoporosis has been submitted to the Food and Drug Administration by UT Southwestern. Once approved, the drug should cost only about $1 a day, making it a very cost-effective osteoporosis treatment, Pak said.

The randomized trial involved 110 patients at UT Southwestern and Scott & White Clinic in Temple, Texas. The two nonrandomized trials included 186 patients at UT Southwestern and nine other sites, including the Cleveland Clinic Hospital, Indiana University School of Medicine,

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Medical University of South Carolina College of Medicine, University of North Texas Health Science Center, Texas Woman's University, The University of Texas at Tyler, Medical City-Dallas Hospital, Methodist Hospitals of Dallas and Scott & White Clinic.

In the randomized trial, women in the treated group took 25 milligrams of sodium fluoride, embedded in a wax matrix to slow its release, twice daily. They also took 400 mg of calcium as calcium citrate twice daily. The fluoride plus calcium citrate was administered for 12 months, followed by two months of calcium citrate alone, in repeated sequence. Women in the placebo group took a placebo and calcium citrate. All patients were postmenopausal women with at least one spinal fracture and an average of three when they entered the study.

Blood fluoride level in the fluoride-treated group was kept within the effective and safe range. The spinal fracture rate in the treated group declined approximately 70 percent, and the fracture-free rate in the treated group was 85.4 percent, compared to 56.9 percent in the placebo group. Spinal bone mass in the treated group increased by 4.8 percent every year for four years. Hip bone density rose by 2.4 percent per year. Frequency and severity of back pain dropped. Women in the fluoride group had no hip fractures, microfractures or gastric ulcers, which have been reported with other forms of fluoride in the past. They sustained only one-third the height loss of the placebo group.

In the combined 240 fluoride-treated patients from all trials, spinal fractures were virtually eliminated by treatment in those with mild to moderate bone loss (defined as loss of less than 35 percent of spinal bone mass). The spinal fracture rate decreased by 83 percent, and only 4.5 percent had new fractures. In those with severe bone loss (more than 35 percent of spinal bone mass), a less marked but still significant reduction in spinal fracture rate of 46 percent occurred. Laboratory analysis using biochemical, histological, biophysical and radiological tests performed by Dr. Joseph Zerwekh and Dr. Peter Antich at UT Southwestern showed that slow-fluoride improved the quantity as well as quality of bone. It significantly increased bone formation and slowed bone resorption — the process by which bone is destroyed — without affecting bone mineralization. Moreover, the architecture of spongy bone improved, especially in patients with mild to moderate bone loss.

"We not only found more bone, but unexpectedly, what appears to be stronger bone," Pak said.

Authors of today's *Annals of Internal Medicine* article in addition to Pak are

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Dr. Khashayar Sakhaee, Dr. Veronica Piziak, Beverley Adams-Huet, Roy D. Peterson and John R. Poindexter. Sakhaee is a professor in internal medicine and the BeautiControl Cosmetics Inc. Professor in Mineral Metabolism and Osteoporosis at UT Southwestern. Piziak is professor of medicine and director of endocrinology at Scott & White Clinic. Adams-Huet is a biostatistician at UT Southwestern.

A paper summarizing the overall results of slow-release sodium fluoride appears in the September issue of *Trends in Endocrinology*. It is co-authored by Pak, Zerwekh and Antich. Zerwekh is the Frederic C. Bartter Professor in Vitamin D Research at UT Southwestern. Antich is the Wechun Pak Professor of Bone Biophysics.

Dr. Judith Vaitukaitis, head of the National Institutes of Health's National Center for Research Resources (NCRR), called Pak's findings exciting. "Any inroad to effectively prevent, reverse or stabilize osteoporosis takes a major step forward in combating this disease, which is so devastating to older women," she said.

The NCRR of the NIH funds the General Clinical Research Center where Pak has conducted much of his studies for many years. UT Southwestern's osteoporosis research also was funded in part by the NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases.

The innovative slow-release preparation of sodium fluoride was formulated by Mission Pharmacal Co. of San Antonio, Texas, to meet Pak's needs and FDA specifications. It delivers the fluoride in a honeycomb wax tablet that allows the mineral to bypass the stomach. Released slowly in the intestines, the fluoride is absorbed slowly without forming hydrofluoric acid, thus avoiding the gastrointestinal problems associated with fluoride therapy in the past and maintaining nontoxic fluoride levels in blood and bones. Once approved by the FDA, slow-release sodium fluoride is to be marketed by Mission.

Calcium supplementation is essential to fluoride treatment of osteoporosis, in order to allow mineralization of bone matrix or collagen stimulated by fluoride to form. Ultradense calcium citrate was chosen because it is readily absorbed and easily tolerated, Pak explained.

The calcium citrate supplement used in conjunction with slow-release sodium fluoride in his clinical trials also was formulated by Mission Pharmacal. It is a tablet, an over-the-counter product marketed under the brand name, Citracal.

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Charles Y.C. Pak, M.D.

After earning his medical degree and completing his internship and residency in internal medicine at the University of Chicago, Dr. Charles Pak joined the National Institutes of Health in 1963. In 1965 he joined Dr. Frederic Bartter as a senior investigator in the Endocrinology Branch of the NIH's National Heart and Lung Institute.

Since 1972 Dr. Pak has been at The University of Texas Southwestern Medical Center at Dallas. Currently he holds the Distinguished Chair in Mineral Metabolism and the Donald W. Seldin Professorship in Clinical Investigation. He is professor of internal medicine and director of the Center for Mineral Metabolism and Clinical Research.

Throughout his career, Dr. Pak has devoted himself to the study of kidney stones and osteoporosis. He has developed three FDA-approved orphan drugs for kidney stones, elucidated metabolic causes for stone formation and devised a multi-test kit for individuals at risk for forming kidney stones. During the past 13 years, he has concentrated on efforts to find an effective but safe use of fluoride. Recently he established a national training program in clinical research for young physicians.

Dr. Pak has published more than 430 scientific articles. In 1987 he received the Distinguished Contribution Award from the American Urological Association. In 1988 he was recognized with the United States Public Service Award for Exceptional Achievement in Orphan Products Development and the Bartter Award from the American Society for Bone and Mineral Research.

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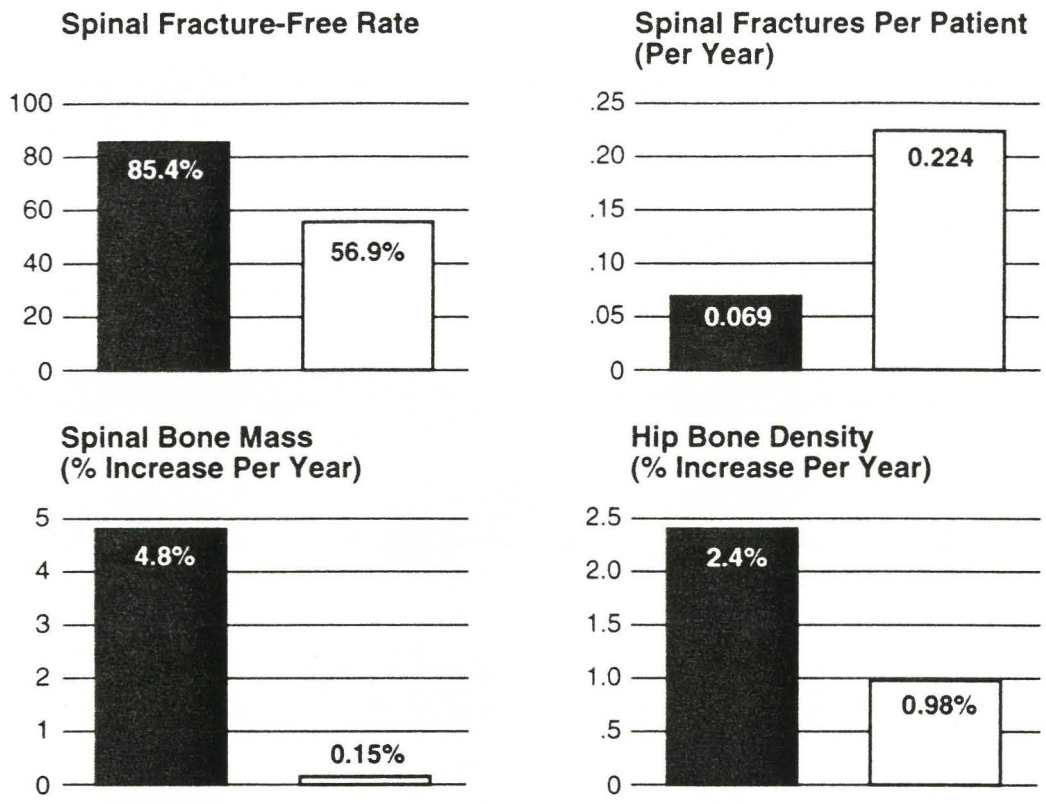
OSTEOPOROSIS TREATMENT

Slow-Release Fluoride/Calcium Citrate

Fluoride Group
Placebo Group



Results of randomized trials of slow-release sodium fluoride supplemented with calcium citrate in 54 postmenopausal women with established osteoporosis, compared to 56 taking placebo.