TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS WITH SLOW-RELEASE SODIUM FLUORIDE. FINAL REPORT OF A RANDOMIZED CONTROLLED TRIAL
C Y C Pak, K Sakhaee, B Adamshuet, V Piziak, R D Peterson and J R Poindexter
Dallas, Texas, USA

Abstract from Annals of Internal Medicine 123 (6) 401-408 1995

Objective: To test whether slow-release sodium fluoride inhibits spinal fractures and is safe to use.

Design: Placebo-controlled randomized trial.

Interventions: Slow-release sodium fluoride, 25 mg twice daily, in four 14-month cycles (12 months receiving sodium fluoride followed by 2 months not receiving it) compared with placebo. Calcium citrate, 400 mg calcium twice daily, continuously in both groups.

Patients: 48 of 54 patients who received sodium fluoride and 51 of 56 patients who received placebo completed at least 1 year of the study. All patients had postmenopausal osteoporosis.

Results: Compared with the placebo group, the fluoride group had a lower individual vertebral fracture rate (0.064 ± 0.182 per patient-year compared with 0.205 ± 0.297 per patient-year; P = 0.002), a higher unadjusted fracture-free rate (85.4% compared with 56.9%; P = 0.001), and a greater survival estimate (relative risk, 0.3 [95% CI, 0.12 to 0.76]) for new fractures. The recurrent spinal fracture rate did not differ between the two groups. The fluoride group had a substantial increase in L2-L4 bone mass of 4% to 5% per year for 4 years, a mean increase in femoral neck bone density of 2.38% ± 3.33% per year, and no change in radial shaft bone density. The frequency with which minor side effects and appendicular fractures occurred was similar in the two groups; no patients developed microfractures or gastric ulcers.

Conclusion: Slow-release sodium fluoride and calcium citrate administered for 4 years inhibits new vertebral fractures (but not recurrent fractures), augments spinal and femoral neck bone mass, and is safe to use.

Key words: Calcium compounds; Delayed-action preparations; Fractures; Osteoporosis, postmenopausal; Sodium fluoride.

Reprints: C Y C Pak, University of Texas, Center for Mineral Metabolism and Clinical Research, 5323 Harry Hines Blvd, Dallas, TX 75235 USA.

FLUOROSIS: EXPERIENCE BASED ON TWO CASES
I Tollefsen, G Duus and F Johannessen
Stavanger, Norway

Abstract from Tidsskrift for Den Norske lægeforening (Journal of the Norwegian Medical Association) 115 (21) 2648-2651 1995

Since 1961 sodium fluoride has been an alternative in the treatment of osteoporosis, although there is still some difference of opinion between endocrinologists regarding the effect on pain and occurrence of fracture of the vertebral column.

Two cases are reported, both treated for postmenopausal osteoporosis with calcium, vitamin D and sodium fluoride for longer periods over many years, and with good effect on pain and tendency to lumbar vertebral body fracture. In both patients the diagnosis of skeletal fluorosis was delayed for several years, mainly because information about this treatment never reached the radiologist. When the
diagnosis was eventually established after the radiologist himself had made inquiries to the referring physician, the patients had in the meanwhile undergone several unnecessary supplementary examinations because of suspected cancer metastasis.

Key words: Fluoride therapy; Osteoporosis; Skeletal fluorosis; Sodium fluoride.
Reprints: I Tollefsen, Department of Radiology, Central Hospital Rogaland, 4011 Stavanger, Norway.

**FLUORIDE REDUCES BONE STRENGTH IN OLDER RATS**

C H Turner, K Hasegawa, W Zhang, M Wilson, Y Li and A J Dunipace
Indianapolis, Indiana, USA

Abstract from *Journal of Dental Research* 74 (8) 1475-1481 1995

In response to recent concerns about the effect of water fluoridation on hip fracture rates, we studied the influence of fluoride intake on bone strength. Four groups of rats were fed a low-fluoride diet *ad libitum* and received 0, 5, 15, or 50 ppm of fluoride in their drinking water. Animals were euthanized after 3, 6, 12, or 18 months of treatment. Mechanical strength of the right femur was measured by three-point bending. Fluoride content for the left femur was measured, and static histomorphometric measurements were made on a lumbar vertebra. Femoral failure load was not significantly decreased in rats treated for 3 and 6 months, but was decreased as much as 23% in rats treated 12 and 18 months at 50 ppm fluoride. Extrapolation from regression equations predicted that older rats lose 36% of femoral bone strength when bone fluoride content is increased from 0 to 10,000 ppm, while younger rats will lose only 15%. Thus, the decreased strength appeared to be due to the combined effects of fluoride intake and age on bone tissue and was not associated with a decrease in bone density or mineralization defects. There were only small effects of fluoride on bone histomorphometry. Fluoride intake at high levels had no negative effects on bone mineralization. Fluoride intake was associated with slight increases in trabecular bone volume and trabecular thickness, but these effects could not be demonstrated consistently. The mechanism by which large amounts of fluoride affect bone strength more severely in older animals is unknown.

Key words: Bone; Fluoride; Rats.
Reprints: C H Turner, Indiana University, School of Medicine, Department of Orthopaedic Surgery, 541 Clin Dr, Indianapolis, IN 46202 USA.

**A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL FOR FLUORIDE UPTAKE BY BONE**

H V Rao, R P Beliles, G M Whitford and C H Turner
Hartford, Connecticut, USA

Abstract from *Regulatory Toxicology and Pharmacology* 22 (1) 30-42 1995

A sex-specific, physiologically based pharmacokinetic (pbpk) model has been developed to describe the absorption, distribution, and elimination of fluorides in rats and humans. Growth curves generated by plotting mean body weights (kg) against age (weeks or years) are included in the simulation model to allow the integration of chronic fluoride exposure from birth to old age. The model incorporates age and body weight dependence of the physiological processes that control the
uptake of fluoride by bone and the elimination of fluoride by the kidneys. Six compartments make up the model. These are lung, liver, kidney, bone, and slowly and rapidly perfused compartments. The model also includes two bone subcompartments: a small, flow-limited, rapidly exchangeable surface bone compartment and a bulk virtually nonexchangeable inner bone compartment. The inner bone compartment contains nearly all of the whole body content of fluoride, which, in the longer time frame, may be mobilized through the process of bone modeling and remodeling. The model has been validated by comparing the model predictions with experimental data gathered in rats and humans after drinking water and dietary ingestion of fluoride. This physiological model description of absorption, distribution, and elimination of fluoride from the body permits the analysis of the combined effect of ingesting and inhaling fluorides on the target organ, bone. Estimates of fluoride concentrations in bone are calculated and related to chronic fluoride toxicity. The model is thus useful for predicting some of the long-term metabolic features and tissue concentrations of fluoride that may be of value in understanding positive or negative effects of fluoride on human health. In addition, the pbpk model provides a basis for across-species extrapolation of the effective fluoride dose at the target tissue, bone, in the assessment of risk from different exposure conditions.

Key words: Bone; Fluoride uptake; Physiologically based pharmacokinetic model.
Reprints: H V Rao, Department of Public Health and Addiction Services, 150 Washington St, Hartford, CT 06106 USA.

OSTEOPOROSIS: DRUG AND NONDRUG THERAPIES FOR THE PATIENT AT RISK [REVIEW]

C L Gamble
Fort Smith, Arizona, USA

Abstract from Geriatrics 50 (8) 39-43 1995

Preventing bone loss and avoiding fractures are the most effective therapies for osteoporosis. Nondrug measures include weight-bearing exercise, adequate calcium intake, and the prevention of falls. Estrogen replacement therapy can protect bone from rapid demineralization typical of the early post-menopausal period. New research has provided more data on estrogen's safety and efficacy. Calcitonin is an option when estrogen is contraindicated. Although calcitonin requires frequent injections, it does provide some analgesic effect for patients with osteoporosis-related fracture. Fluoride and etidronate have shown promise but remain investigational due to questions about long-term effects on bone mass. Potent third-generation bisphosphonates are being studied and may be available soon.

Key words: Drug therapies; Non-drug measures; Osteoporosis.
Reprints: C L Gamble, Cooper Clinic Osteoporosis Center, Fort Smith, AR USA.
Pretreatment with Low Doses of Norethindrone Potentiates the Osteogenic Effects of Fluoride on Human Osteosarcoma Cells

J. Takada, D. J. Baylink and K. H. W. Lau
Loma Linda, California, USA


We recently reported that picomolar doses of norethindrone (NET), a synthetic analog of 19-nortestosterone, significantly stimulated human TE85 osteosarcoma cell proliferation, differentiation, and activity in vitro. In the present study, we investigated the possibility that NET interacts with another osteogenic agent, i.e., fluoride, to stimulate human TE85 osteosarcoma cell proliferation, differentiation, and activities. Bone cell proliferation as measured by the stimulation in [H-3]thymidine incorporation. Differentiation was monitored by the increase in alkaline phosphatase-specific activity. Osteoblastic activity was assessed by the stimulations in collagen synthesis and in osteocalcin secretion (in the presence of 1 nM 1,25-dihydroxyvitamin D-3). When the human TE85 cells were incubated with mitogenic doses of NET and fluoride concurrently, the stimulatory effects of the two agents on these parameters exhibited no significant interaction. The enhancing effect of NET on the osteogenic effect of fluoride was not due to a shift of the fluoride dose response curve. Pretreatment with NET for 24 h followed by a treatment with a mitogenic dose (i.e., 100 µM) of fluoride for an additional 24 h significantly and synergistically potentiated the effects of fluoride on the [H-3]thymidine incorporation, alkaline phosphatase-specific activity, collagen synthesis, and osteocalcin secretion, compared with those with the subsequent vehicle (0.05% ethanol) treatments. In contrast, pretreatment, with fluoride for 24 h before the addition of NET for 24 h did not produce significant synergistic stimulations in the test parameters. Pretreatment of TE85 cells with the same doses of dihydrotestosterone or progesterone prior to treatment with fluoride under the same conditions did not induce synergistic potentiation of fluoride in [H-3]thymidine incorporation, suggesting that the synergistic interaction with fluoride is probably not a common property of anabolic sex steroids. In summary, we found that: (1) the osteogenic effects of fluoride and NET were additive when cells were treated with both agents concurrently; (2) a 24-h pretreatment with picomolar doses of NET potentiated the osteogenic actions of fluoride in human TE85 osteosarcoma cells; and (3) pretreatment with NET produced a subsequent fluoride response that was synergistic. In conclusion, these findings led us to speculate that the osteogenic actions of NET and fluoride act through different mechanisms, and that NET at low doses has a permissive effect on the osteogenic effects of fluoride, and as such NET may be used in concert with fluoride to increase osteoblast proliferation, differentiation, and activity.

Key words: Bone; Fluoride; Norethindrone; Osteogenic; Osteosarcoma.
Reprints: K. H. W. Lau, Jerry L. Pettis Memorial Veterinary ADM Medical Center, Mineral Metabolism Unit 151, 11201 Benton St, Loma Linda, CA 92357 USA.
PRESENT AND FUTURE OF OSTEOPOROSIS THERAPY
E Seeman, C Tsalamandris, S Bass and G Pearce
Heidelberg, Victoria, Australia
Abstract from Bone 17 (2) Suppl. S23-S29 1995

In the 50-year "modern" history of osteoporosis, there have been about 17 anti-fracture studies with sufficient attention to design to allow inference regarding efficacy. Antivertebral fracture efficacy has been reported with etidronate, estrogen patch, calcitonin, and 1,25-dihydroxyvitamin D. Two studies using fluoride were positive, and two were negative. Hip fractures have been neglected. One study showed efficacy of hip protectors, one showed efficacy of vitamin D and calcium in nursing home dwellers. The source of most hip fractures is the community. One community based antihip fracture efficacy study using annual injections of vitamin D was positive. There have been no antivertebral or antihip fracture studies in men, or in corticosteroid-related osteoporosis in men or women. Lack of independently repeated demonstration of efficacy, small fracture numbers, and data pooling in some of these (the best) studies leave great uncertainty. Estrogen and bisphosphonates appear to be the best options at this time. New data suggest that calcium supplementation is likely to reduce the rate of bone loss and perhaps reduce fracture rates. The challenge is to maintain and restore the constituents of bone mineral density (BMD), that is: to promote periosteal and endosteal bone formation; reduce endosteal bone resorption and cortical porosity; and increase trabecular thickness, number, and connectivity. There are many opportunities, for instance, intermittent parathyroid hormone (PTH) increases bone strength and, with estrogen, may increase connectivity. The anabolic effects of PTH may be partly mediated by IGF-1. IGF-1 increases periosteal, endosteal, and trabecular bone formation, cortical and trabecular width, and trabecular and endocortical connectivity. With bisphosphonate, IGF-1 may increase bone area and strength as the bisphosphonate decreases medullary area while IGF-I increases subperiosteal area. Anabolic effects of fluoride warrant further study provided that the study design addresses the issue of bone strength, the narrow toxic therapeutic window, and cortical bone loss. Aluminum, a constituent of zeolite, has anabolic effects which may be partly mediated by TGF-P. Prostaglandin E(2) increases periosteal and endosteal bone formation but may increase cortical porosity. More data are needed regarding these growth factors, silicon compounds, strontium salts, and flavinoids. The effects of medroxyprogesterone and 19-norprogestins on BMD have not been compared. Raloxifene, a new estrogen agonist free of endometrial hyperplastic effects, is being studied. Most treated individuals with osteoporosis (i.e., low BMD with or without a fracture) will not suffer a fracture so treatment must be safe. Success - absence of fracture - will be measured by the epidemiologist because it is difficult to distinguish efficacy from chance in an individual as the peak incidence of fractures in the community is usually only about 1-4/100 per year.

Key words: Osteoporosis; Study design; Treatment.
Reprints: E Seeman, Austin Hospital, Department of Endocrinology, Heidelberg, Vic 3084, Australia.
NO INCREASES IN CHROMOSOME ABERRATIONS IN HUMAN DIPLOID FIBROBLASTS FOLLOWING EXPOSURE TO LOW CONCENTRATIONS OF SODIUM FLUORIDE FOR LONG TIMES

T Tsutsui, Y Tanaka, Y Matsudo, A Uehama, T Someya, F Hamaguchi, H Yamamoto and M Takahashi
Tokyo, Japan

Abstract from Mutation Research - Environmental Mutagenesis and Related Subjects 335 (1) 15-20 1995

To study whether exposure to fluoride at low concentrations for long times induces chromosome aberrations in human cells, human diploid fibroblasts in the quiescent phase were treated with sodium fluoride (NaF) at 1-10 μg/mL (equivalent to fluoride ion at 0.45-4.5 ppm) for 1-3 weeks. Quiescent cells were obtained by a 10-day culture in medium containing 1% serum following overnight incubation of cells in the logarithmic phase. Significant levels of cytotoxicity, as determined by a decrease in the number of cells, were not induced by treatment of the cells with NaF at 5 or 10 μg/mL for 1-3 weeks. No increase in the frequency of chromosome aberrations was elicited in cultures treated for 1-3 weeks with NaF over the range of doses examined. In contrast, a dose-dependent increase in the frequency of chromosome aberrations was observed in cultures treated with N methyl-N'-nitro-N-nitrosoguanidine, used as a positive control. The results indicate that fluoride might be not clastogenic to human fibroblasts when exposed at low levels, equivalent to those in the communal water supplies.

Key words: Chromosome aberrations; Clastogenicity; Human diploid fibroblasts; Sodium fluoride.

Reprints: T Tsutsui, University of Tokyo School of Dentistry, Department of Pharmacology, Chiyoda Ku, 1-9-20 Fujimi, Tokyo 102, Japan.

LONG TERM EXPOSURE TO FLUORIDE IN DRINKING WATER AND SISTER CHROMATID EXCHANGE FREQUENCY IN HUMAN BLOOD LYMPHOCYTES

Y Li, C K Liang, B P Katz, E J Brizendine and G K Stookey
Indianapolis, Indiana, USA

Abstract from Journal of Dental Research 74 (8) 1468-1474 1995

The genetic toxicity of fluoride has been investigated extensively by various test systems. However, results obtained have been inconsistent. Fluoride has been reported to be non-genotoxic, genotoxic, and synergistic or antagonistic with certain mutagens. To date, there are no published human studies on the genotoxicity of fluoride. The purpose of this investigation was to determine genotoxic risks of long-term exposure to various concentrations of fluoride in drinking water in humans with normal or inadequate nutrition. Six groups of subjects with either normal or inadequate nutritional intakes were selected from areas of approximately 0.2, 1.0, or 4.8 ppm (10.5, 52.6, or 252.6 μmol/L) fluoride in water. The subjects had been continuous residents in the area for at least 5 years. Samples of drinking water, plasma, and urine were analyzed for fluoride content. Blood lymphocytes were
examined to determine the frequency of sister chromatid exchange (SCE). Blood chemistry and electrolytes were also analyzed. The results showed that average daily fluoride intake as well as urine and plasma fluoride levels increased with increase in the fluoride content of the drinking water. The blood chemistry and electrolyte values were within the normal range for all populations, but several parameters were significantly different. While the numerical differences were small, the subjects with low fluoride in the water (0.11 and 0.23 ppm or 5.8 and 12.1 μ mol/L) had significantly higher SCE frequencies than those with higher fluoride exposures. Reasons for the reduced SCE frequency in subjects with higher fluoride exposure are unclear; however, the data demonstrated that long-term exposure to fluoride in the drinking water, even at an elevated level, does not have genotoxic effects in humans.

Key words: Genotoxicity; Human blood lymphocytes; Sister chromatid exchange; Water fluoride.

Reprints: Y Li, Indiana University, School of Dentistry, 1121 W Michigan St, Indianapolis, IN 46202 USA.

[The above research, which was supported by a grant from the US government's National Institute of Dental Research, was presented at the XXth Conference of the International Society for Fluoride Research, Beijing, in September 1994. Since then other studies - one of them also presented at the XXth ISFR Conference - reporting human genetic damage associated with endemic fluorosis, have been published (Fluoride 27 215-219 1994, and Fluoride 28 125-127 1995). The different research designs partly account for the differing conclusions. The studies published in Fluoride compared SCE rates of normal, non-fluorotic, patients with those of patients with symptoms of fluorosis. The above NIDR study compared SCE rates of residents, rather than normal and fluorotic individuals, from areas with differing water fluoride levels. - JC]

SERUM LIPOPROTEIN LEVELS IN GENETICALLY HYPERCHOLESTEROLAEMIC RICO RATS:
EFFECTS OF A HIGH-SUCROSE-CHOLESTEROL DIET WITHOUT OR WITH ALTERED MAGNESIUM AND FLUORIDE CONTENT

H Luoma, P Alakuijala, A Korhonen, T Nevalainen, M Kuronen and M Jauhiainen
Kuopio, Finland


Genetically hypercholesterolaemic Rico rats (male, 6 weeks old) were randomly distributed into 6 experimental groups. The zero-time basal group A was sacrificed at the start of the experiment while the other groups were fed for 6 weeks and then sacrificed. Group B was fed a stock diet. Control group C was fed a high-sucrose (45%) diet with 0.5% added cholesterol. In the diet of group D, only the magnesium (Mg) content was reduced from the level of group C (883 ppm) to 200 ppm. The diet of group E was the same as that of group D with the addition of 12 ppm of fluoride (F) and the diet of group G was the same as that of group E, but with its Mg content elevated from 200 ppm to 300 ppm. Analysis of aortic blood samples, taken before sacrifice, indicated significant increases in total serum cholesterol (p<0.01), very low density lipoprotein (VLDL) (p < 0.001) and low density lipoprotein (LDL), (p < 0.001) cholesterol, and a trend to lower high density lipoprotein (HDL) cholesterol in group C, as compared to group B. Significantly lower total (p<0.05), VLDL (p<0.01) and LDL (p<0.01) triglycerides were observed in group C when
compared to group B. The LDL phospholipids were significantly higher in group C (p < 0.001) than in group B. When cholesterol levels in groups D, E and G were compared with group C, the VLDL cholesterol in group E and the LDL cholesterol in group G were slightly but significantly (p < 0.05) reduced, while total cholesterol and the other subfractions were unaltered. The LDL triglycerides of groups E and G were significantly smaller still than the already small fraction in group C. The VLDL triglyceride in group E was significantly lower than that of group C (35% reduction, p < 0.001), D and G (p < 0.05). Phospholipids were slightly but significantly reduced in the VLDL fraction of group E and in the LDL fraction of group G (p < 0.05 and 0.01, respectively), as compared to those of group C.

Key words: Cholesterol; Dietary fluoride; HDL; LDL; Magnesium; Phospholipids; Rico rat; Serum; Triglycerides; VLDL.

RENAL FUNCTION IN PATIENTS WITH HIGH SERUM FLUORIDE CONCENTRATIONS AFTER PROLONGED SEVOFLURANE ANESTHESIA

H Higuchi, H Sumikura, S Sumita, S Arimura, F Takamatsu, M Kanno and T Satoh
Saitama, Japan

Abstract from Anesthesiology 83 (3) 449-458 1995

Background: In studies of methoxyflurane-induced nephrotoxicity, renal-concentrating impairment has been observed only when serum inorganic fluoride concentrations exceed 50 μM. Prolonged sevoflurane anesthesia can result in serum inorganic fluoride concentrations in excess of 50 μM. The authors compared renal function after prolonged sevoflurane anesthesia with that after isoflurane anesthesia. In addition, they measured urinary excretion of N-acetyl-beta-glucosaminidase (NAG), a sensitive index of renal tubular damage, during the S-day period after anesthesia.

Methods: Thirty-four healthy patients who underwent either sevoflurane (23 patients) or isoflurane (11 patients) anesthesia at a total gas flow of 61/min for orthopedic surgery scheduled to last at least 5 h were studied. At 16.5 h after cessation of anesthesia, patients were administered 10 units of vasopressin, and urine was collected frequently thereafter for evaluation of urinary osmolality. In addition, urinary excretion of NAG was measured before and on days 1-3 after anesthesia. Based on whether peak fluoride concentrations exceeded 50 μM, 23 patients anesthetized with sevoflurane were assigned to a sevoflurane (high) (> 50 μM) group or a sevoflurane (low) (< 50 μM) group.

Results: The eight patients in the sevoflurane (high) group had a mean peak fluoride concentration of 57.5 ± 4.3 μM. A significant, albeit weak, inverse correlation was found between peak fluoride concentration and maximal urinary osmolality after the injection of vasopressin (r = -0.42, P < 0.05). Mean maximum urinary osmolality tended to be lower in the sevoflurane (high) group (681 ± 60 m Osm/kg) than in the other two groups after administration of vasopressin, although the difference among the three groups did not quite reach statistical significance (P = 0.068). One patient had a transient concentrating defect (maximum urinary osmolality = 390 m Osm/kg) on day 1 after anesthesia. Urinary excretion of NAG in both the
sevoflurane (high) and sevoflurane (low) groups was greater on days 2 and 3 after anesthesia than before anesthesia. The increase in urinary NAG excretion was dose related with sevoflurane, but there was no difference in results of routine laboratory renal tests on days 2 and 3 after anesthesia among the three groups.

Conclusions: The authors concluded that sevoflurane anesthesia results in increased serum fluoride concentration, a tendency toward decreased maximal ability to concentrate urine, and increased excretion of NAG. However, the increase in urinary NAG excretion was not indicative of clinically significant renal damage in these patients with no preexisting renal disease.

Key words: Anesthetics; Fluoride ions; Isoflurane; Kidney function; Nephrotoxicity; Sevoflurane; Urinary concentrating mechanism; Vasopressin.

Reprints: H Higuchi, National Defence Medical College, Department of Anesthesiology, 3-2 Namiki, Tokorozawa, Saitama 359, Japan.

RENAL FUNCTION AND SERUM FLUORIDE CONCENTRATIONS IN PATIENTS WITH STABLE RENAL INSUFFICIENCY AFTER ANESTHESIA WITH SEVOFLURANE OR ENFLURANE

P F Conzen, M Nuscheler, A Melotte, M Verhaegen, T Leupolt, H Vanaken and K Peter Munich, Germany

Abstract from Anesthesia and Analgesia 81 (3) 569-575 1995

Sevoflurane is metabolized to hexa-fluoro-isopropanol and inorganic fluoride by the human liver. Its use as an anesthetic may lead to peak plasma fluoride concentrations exceeding those seen after enflurane. Although there is no nephrotoxicity after sevoflurane anesthesia in humans with normal kidneys, those with chronically impaired renal function might be at increased risk because of increased fluoride load due to prolonged elimination half-life. In this study, measures of renal function after sevoflurane anesthesia were compared to those after enflurane in patients with chronically impaired renal function. Forty-one elective surgical patients with a stable preoperative serum creatinine concentration greater than or equal to 1.5 mg/dL were randomly allocated to receive sevoflurane (n = 21) or enflurane (n = 20) at a fresh gas inflow rate of 4 L/min for maintenance of anesthesia. Serum fluoride concentrations were measured by ion-selective electrode. Renal function (creatinine, urea, sodium, osmolality) was assessed in serum and urine preoperatively and for up to 7 days postoperatively. Peak serum inorganic fluoride concentrations were significantly higher after sevoflurane than after enflurane anesthesia (25.0 ± 2.2 vs 13.3 1.1 μM; mean ± SEM). Laboratory measures of renal function remained stable throughout the postoperative period in both groups. No patient suffered a permanent deterioration of preexisting renal insufficiency and none required dialysis. Thus, neither sevoflurane nor enflurane deteriorated postoperative renal function in these patients with preexisting renal insufficiency. There is no evidence that fluoride released by metabolism of sevoflurane metabolism worsened renal function in these patients with stable, permanent serum creatinine concentrations more than 1.5 mg/dL. Our data also suggest that the peak fluoride concentrations measured in peripheral blood may not be a good predictor of nephrotoxic potential after sevoflurane anesthesia in these patients.

Key words: Anesthesia; Fluoride; Kidney function; Sevoflurane.

Reprints: P F Conzen, University of Munich, Klinikum Grosshadern, Institute of Anesthesiology, Marchioninistr 15, D-81377 Munich, Germany.
Much of the dental literature on fluoride effects continues to assume a dental "optimal" (1 ppm) water fluoride level. Much contains little original research of interest to other researchers. Heading the following list is the subject of our last editorial: an inaccurate personal attack on a prominent opponent of water fluoridation. The second on the list reports a non-blind examination of 344 children "residing in communities with negligible (NF: 0.2 ppm), optimal (OPF: 1.0 ppm), and four-times optimal (4X OPF: 4.0 ppm) naturally occurring fluoride in their water systems." Predictably it concludes: "The ingestion of water containing 1 ppm or less fluoride during the time of tooth development may result in dental fluorosis, albeit in its milder forms. However, in these times of numerous products containing fluoride being available, children ingesting water containing 1 ppm fluoride continue to derive caries protection compared to children ingesting water with negligible amounts of fluoride. Thus, the potential for developing a relatively minor unesthetic condition must be weighed against the potential for reducing dental disease." After this list we reprint some of the more interesting abstracts, commenting on one of them. - JC


DENTAL CARIES EXPERIENCE AND DEFECTS OF DENTAL ENAMEL AMONG 12-YEAR-OLD CHILDREN IN NORTH LONDON, EDINBURGH, GLASGOW AND DUBLIN M C Downer, A S Blinkhorn, R D Holt, C Wright and C Attwood London, England

Abstract from Community Dentistry and Oral Epidemiology 22 283-285 1994

A multi-center study of caries experience and defects of dental enamel was conducted among 12-year-old children in north London, Edinburgh, Glasgow and Dublin. None of the cities had water fluoridation except Dublin, which was included in the national program introduced in the Republic of Ireland in 1964. A random sample of children was drawn from state schools in each location and identical methods of clinical examination were used throughout under the same standardized conditions. All examiners were trained and calibrated with a reference examiner and achieved high levels of inter- and intra-examiner consistency. Mean DMFT values for the 4 cities were 1.27 (London), 1.39 (Edinburgh), 2.70 (Glasgow) and 1.48 (Dublin) \( P < 0.001 \). Proportions of subjects free from caries in the same order were, 50, 47, 24 and 43\% \( P < 0.001 \), and child prevalence of diffuse opacities, 28,
29, 7 and 17% ($P < 0.001$), respectively. The relatively low caries levels recorded in London and Edinburgh (lower than Dublin) were considered to be related most probably to fluoride effects other than water fluoridation.

Key words: Defects of dental enamel; Dental caries; Epidemiology; Fluoride.

Reprints: M C Browne, Department of Dental Health Policy, Institute of Dental Surgery, Eastman Dental Hospital, 256 Gray’s Inn Road, London WC1X 8LD, England.

Comment: Although two of the three unfluoridated cities surveyed had less tooth decay than the fluoridated city surveyed, the authors in their Discussion section argued that other forms of fluoride exposure were probably responsible for the reduced decay. Because their results also showed that “diffuse enamel opacities” (their term for dental fluorosis) were more prevalent in the unfluoridated cities with low tooth decay rates than in the high-decay unfluoridated city and the fluoridated city, they concluded that greater use (and swallowing) of fluoridated toothpaste could be a cause. Though they reported that the low-decay unfluoridated cities were more affluent, with possibly differing “dietary propensities”, they did not discuss the possibility that better nutrition, rather than differing fluoride exposure, could have contributed to the lower decay rates. - JC

THE EFFECT OF A LOW FLUORIDE CONTAINING TOOTHPASTE ON THE DEVELOPMENT OF DENTAL CARIES AND MICROBIAL COMPOSITION USING A CARIES GENERATING MODEL DEVICE IN VIVO

L G Petersson, S Edwardsson, G Koch, J Kurol and A Lodding
Halmstad, Sweden

Abstract from Swedish Dental Journal 19 (3) 83-94 1995

The purpose of the study was to evaluate the effect of daily use of a low fluoride containing toothpaste (250 ppm F) on the uptake of fluoride and development of enamel lesions as well as the prevalence of lactobacilli and mutans streptococci in dental plaque compared to the use of placebo toothpaste. 16 children were selected with homologous premolar teeth. The teeth were cemented with orthodontic bands ad modum Ogaard for plaque accumulation and enamel lesion development. The plaque accumulated during 4 weeks was collected and analysed for lactobacilli and mutans streptococci. The teeth were further analysed by secondary ion mass spectrometry (SIMS), determining the concentration profiles of fluoride and other elements in the outermost enamel and in the lesion. The results show that although significant amounts of fluoride were taken up in the surface enamel from the fluoride toothpaste, the extent of the lesions was not influenced compared to teeth brushed with a non F-toothpaste. Neither were microbiological differences in the dental plaque found between the groups. An interesting observation was that early demineralization of enamel took place without detectable levels of mutans streptococci in the overlaying dental plaque. The conclusion is that fluoride taken up in enamel from F-toothpaste has no significant influence on enamel lesion development if a cariogenic dental plaque with high levels of acid producing microorganisms is continuously attached to the enamel surface.

Key words: Dental caries; Dental plaque; Fluoride toothpaste.

Reprints: Department of Preventive Dentistry, Medical and Dental Center, Halmstad, Sweden.
FORMATION OF PHOSPHATE-CONTAINING CALCIUM FLUORIDE AT THE EXPENSE OF ENAMEL, HYDROXYAPATITE AND FLUORAPATITE

J Christoffersen, M R Christoffersen, J Arends and E S Leonardsen
Copenhagen, Denmark

Abstract from *Caries Research* 29 (3) 223-230 1995

During the caries process complex reactions involving calcium, phosphate, hydrogen and fluoride ions as main species take place. In this study the precipitation and dissolution reactions occurring in suspensions of enamel, hydroxyapatite (HAP) and fluorapatite (FAP) on addition of fluoride were investigated under well-defined conditions. pH and pF were monitored; calcium and phosphate concentrations were measured at selected times; the solid phases were examined by infra-red, X-ray diffraction and transmission electron microscopy. Precipitation of phosphate-containing calcium fluoride crystals, CaF$_2$(P), can cause severe reduction in the calcium ion concentration and release of hydrogen ions from the precipitated phosphate. These reactions result in considerable dissolution of enamel, HAP and even of FAP. More of the added mineral dissolves with 50 mmol/L fluoride than with 10 mmol/L fluoride, mainly due to the greater reduction in calcium ion concentration. This work shows that phosphate-containing calcium fluoride is most likely an important compound to be considered in the caries process.

Key words: Calcium fluoride; Dental enamel; Fluorapatite; Hydroxyapatite.

Reprints: Department of Medical Biochemistry and Genetics, Panum Institute, Copenhagen N, Denmark.

THREE-YEAR RANDOMIZED TRIAL OF PROFESSIONALLY APPLIED TOPICAL FLUORIDE GEL COMPARING ANNUAL AND BIANNUAL APPLICATIONS WITH WITHOUT PRIOR PROPHYLAXIS

D W Johnston and D W Lewis
London, Ontario, Canada

Abstract from *Caries Research* 29 (5) 331-336 1995

The twice yearly application to children’s teeth of acidulated phosphate fluoride (APF) gel in dental trays preceded by a professionally rendered “dental prophylaxis” has become the standard and most commonly used dental chairside procedure for prevention of dental caries. This study was a randomized, 3-year, community-based clinical trial of professionally applied APF gel involving the use and non-use of a prior dental prophylaxis and annual and biannual APF applications for children in age groups 6-7 (n = 176) and 10-11 (n = 153) years initially, who are likely at high risk of future dental caries. The 3-year results of this study show no significant effect on dental caries reduction of either a prior prophylaxis or annual versus biannual APF gel applications. A significant reduction in the frequency of provision of these dental services, limited to high caries risk patients only, is recommended.

Key words: Acidulated phosphate fluoride; Dental caries prevention; Dental prophylaxis; Topical fluoride application.

Reprints: D W Johnston, University of Western Ontario, Health Science Center, Dental Science Bldg Room 1007B, London ON N6A 5C1, Canada.
EFFECT OF LOW LEVELS OF FLUORIDE ON CALCIUM UPTAKE BY DEMINERALIZED HUMAN ENAMEL

C D Gibbs, S E Atherton, E Huntington, R J M Lynch and R M Duckworth
Wirral, England

Abstract from Archives of Oral Biology 40 (9) 879-881 1995

The effect of fluoride (ca. 0.1 parts/10⁶) on calcium uptake by enamel was examined under alternating remineralizing and demineralizing conditions. The remineralizing solutions contained either 0, 0.058, 0.104 or 0.138 parts/10⁶ fluoride (ex NaF), while the demineralizing solutions contained no added fluoride. During the demineralization periods, calcium loss was similar for all groups. However, during the remineralizing periods, all levels of added fluoride were found to promote calcium uptake. Calcium levels taken up by the artificial lesions were found to increase with increasing fluoride concentration in solution, and were independent of surface area of exposed enamel. In the absence of fluoride, even under conditions that are considered to be remineralizing, further demineralization took place.

Key words: Fluoride; Enamel; Demineralization; Remineralization.
Reprints: C D Gibbs, Unilever Dental Research, Quarry Rd E, Wirral L63 3JW, Merseyside, England.

TOOTHPASTE TECHNIQUE: STUDIES ON FLUORIDE DELIVERY AND CARIES PREVENTION.

K Sjogren
Goteborg, Sweden

Abstract from Swedish Dental Journal - Supplement 110 1-44 1995

The aim of the investigations was to evaluate the cariostatic effects of a modified toothpaste technique using fluoride (F) toothpaste. The modification consisted of an active mouthrinse with the toothpaste slurry and a sip of water for one minute after brushing. Toothpaste technique and salivary F concentration after toothbrushing were recorded in a caries active and a caries inactive group. The level of F in whole saliva, the concentration of F in plasma, the effect on demineralised enamel and dentine samples, and the accumulation of F in interdental plaque when using the modified toothpaste technique were studied. In a 3-year clinical trial, 4-year old children were trained in the toothpaste technique. The results showed that in the caries active group, the water rinsing was more thorough and more water was used compared to a caries inactive group. Rinsing with water and eating immediately after toothbrushing decreased the F level in whole saliva. Mouthrinising with either a NaF solution or a slurry of toothpaste foam and water increased the F concentration in saliva compared to when a single or double water rinse was performed. The degree of F absorption in plasma, the accumulation of F in approximal plaque and the interdental clearance after toothbrushing were strongly related to the mode of water rinsing. The degree of demineralisation of enamel and dentine at approximal sites was also related to the mode of water rinsing. The clinical study showed that the cariostatic effect of the modified toothpaste technique resulted in 26% less approximal caries in the test group. It is concluded that a toothpaste technique where a slurry rinse was carried out after brushing increased the efficacy of F toothpaste.

Key words: Dental caries; Dental plaque; Fluoride toothpaste.
Reprints: Department of Cariology, Faculty of Odontology, Goteborg University, Sweden.
CHARACTERIZATION OF FLUOROSED HUMAN ENAMEL BY COLOR REFLECTANCE, ULTRA STRUCTURE, AND ELEMENTAL COMPOSITION

N J Giambro, K Prostak and P K Den Besten
Boston, Massachusetts, USA

Abstract from Caries Research 29 (4) 251-257 1995

Mature fluorosed human enamel has been described as a subsurface enamel hypomineralization, with porosity increasing relative to the degree of fluorosis. The purpose of the current study was to quantitatively measure the color of the fluorosed enamel by light reflectance, and to further characterize the enamel by scanning electron microscopy. Teeth with varying degrees of fluorosis were obtained and divided in groups of mild, moderate and severe fluorosis using Dean's index for fluorosis. The color of the labial enamel surface was measured using a Minolta Chroma Meter CR241 (Minolta, Ramsey, NJ, USA). The teeth were further characterized for elemental composition using an energy-dispersive spectrometer, and imaged in both secondary and backscattered electron modes. The results of this study showed that the moderately and severely fluorosed enamel contained an uneven distribution of areas which were more electron-absorbent with a relatively increased carbon content. The changes in the physical characteristics of the teeth could be quantitated by measurements of light reflectance. The color of the teeth was significantly different between groups, with all groups significantly different than normal.

Key words: Color reflectance; Dental enamel composition; Dental fluorosis; Ultrastructure.

Reprints: N J Giambro, Forsyth Dental Center, 140 Fenway, Boston MA 02115 USA.

EFFECTS OF FLUORIDE-SUPPLEMENTED SUCROSE ON EXPERIMENTAL DENTAL CARIES AND DENTAL PLAQUE pH

T W Cutress, C H Sissons, E I Pearce, L Wong,
K Anderssen and B Angmar-Mansson
Wellington, New Zealand

Abstract from Advances in Dental Research 9 (1) 14-20 1995

Sucrose, 5% and 10% (w/v), supplemented with between 0 and 5 ppm fluoride (F), was tested for its influence in vitro on plaque-induced experimental in vitro enamel caries and plaque pH. Plaque growth on bovine enamel was initiated from saliva inocula and sustained in a multiple plaque growth system for up to 31 days by means of a basal medium with periodic applications of sucrose or sucrose supplemented with F. Change in enamel mineralization was assessed, before and after plaque growth, by microhardness testing and microradiography; pH was monitored with microelectrodes. It was found that enamel demineralization was inversely related to the F concentration in the range 2 to 5 ppm, for both 5% and 10% sucrose. Plaque pH responses were unaffected by the F supplements.

Key words: Dental caries; Dental plaque; Sugar fluoridation.

Reprints: Dental Research Unit, Health Research Council, PO Box 27007, Wellington, New Zealand.
FLUORIDE AND SUGAR INTAKE AMONG ADULTS AND YOUTH IN MAURITIUS: PRELIMINARY RESULTS

S M Lahti, U Uusitalo, E Feskens, U Haw, J Tuomilehto and H Luoma
Kuopio, Finland

Abstract from Advances in Dental Research 9 (1) 21-25 1995

The potential use of different vehicles for delivering fluoride to prevent dental caries has been discussed recently in Mauritius. Water fluoridation was found not to be feasible, and extending the fluoride tablet program would not be easy. Thus, sugar fluoridation as one possibility was considered. For these purposes, the average fluoride and sugar intake was estimated in Mauritius. The results are based on two studies - a Survey on Diet, Health and Lifestyle of Youth in Mauritius (1990) and the Mauritius Diet and Health Survey. Information was collected by trained interviewers using food-frequency and 24-hour-recall questionnaires. The daily total sugar intake, manufactured and natural, was found to be 62 g per day in young people and 50 g per day in adults. In the younger groups, daily frequencies of raw sugar, sweets, and biscuit (cookie) consumption were 1.5, 0.2, and 0.2 times a day, respectively. For adults, the mean daily frequency of consuming sugar-containing foods was 2.6 (SD = 1.3). The daily sucrose intake was rather high, representing about 10% of the daily energy intake. The fluoride levels of foods were calculated by use of Finnish and other available fluoride tables. The mean fluoride intakes per day were 0.64, 0.72, and 0.62 mg per day for 8-17-year-, 18-24-year-, and 30-64-year-old groups, respectively. The median fluoride intake for the oldest group was 0.62 mg/day. The estimated fluoride intake from food did not correspond with the proposed level for the prevention of caries (Murray, 1986) except for the 18-24-year-olds, where it might have been just above the lower recommended limit. However, further data based on analysis of the fluoride contents of Mauritian food samples, especially of whole daily diet, are needed.

Key words: Fluoride intake; Mauritius; Sugar fluoridation; Sugar intake.
Reprints: S M Lahti, WHO Collaborating Centre, Faculty of Dentistry, University of Kuopio, Finland.

EFFECTS ON DEMINERALIZATION OF ENAMEL BY FLUORIDATED SUCROSE: A PILOT STUDY IN AN IN SITU CARIES MODEL

P Carlsson, B Angmar-Mansson, I M Redmo-Emanuelsson and K Anderssen
Malmo, Sweden

Abstract from Advances in Dental Research 9 (1) 9-13 1995

Blocks of human enamel, placed in removable partial dentures, were allowed to acquire natural plaque for seven days and were exposed extra-orally to a cariogenic challenge by repeated periods in a fluoride-sucrose solution. As a control, enamel blocks were exposed extra-orally to a sucrose solution. After two weeks of cariogenic challenge, the blocks were examined for mineral loss by quantitative micro-radiography on thin sections of the enamel. The results from six subjects showed that no significant effect on demineralization could be detected by the addition of fluoride corresponding to fluoride/sugar content of 1 mg/kg, 5 mg/kg, or 10 mg/kg (dry weight). One subject did not develop lesions at all, either with fluoride-sucrose or with sucrose exposure alone.

Key words: Dental caries; Sugar fluoridation.
Reprints: P Carlson, Department of Cariology, University of Lund, Malmo, Sweden.