REDCELL MEMBRANE ALTERATIONS IN HUMAN CHRONIC FLUORIDE TOXICITY

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Abstract from Biochemistry International 23 (4) 639-48 1991

Red cells from humans exposed chronically to toxic levels of fluoride through drinking water showed significant increase in lipid peroxidation and membranous cholesterol and phospholipids. Additionally, electrophoretic patterns of ghost membrane proteins revealed the presence of a new band in the range of 66 Kd and increase in the high molecular weight protein and predominance of bands with a molecular weight of 93 Kd and ≥ 20 Kd. The activities of total, Na+ -K+ -, Mg2+ - and Ca2+ - ATPases were significantly decreased in the red cell ghosts of fluorotic patients.

Key words: Chronic fluoride toxicity; Erythrocytes; Red cells.
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DIACYLGLYCEROL GENERATION IN FLUORIDE-TREATED NEUTROPHILS: INVOLVEMENT OF PHOSPHOLIPASE D

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Abstract from Blood 77 (12) 2746-56 1991

Neutrophils exposed to fluoride ion (F-) respond with a delayed and sustained burst of superoxide anion release that is both preceded by and dependant on the influx of Ca2+ from the extracellular medium. The results of this study demonstrate a similarly delayed and sustained generation of 1,2-diacylglycerol in F--treated neutrophils, over 90% of which was 1,2-diacylglycerol. Diacylglycerol generation was not dependent on the presence of extracellular Ca2+. Conversely, in contrast to results obtained with other agonists, removal of extracellular Ca2+ markedly potentiated synthesis of diacylglycerol in F--treated neutrophils. This effect was accompanied by a corresponding decrease in the recovery of phosphatidic acid. In either the presence or absence of extracellular Ca2+, phosphatidic acid accumulated before diacylglycerol in F--treated cells, suggesting the latter was derived from the former. Consistent with this hypothesis, the phosphatidic acid phosphohydrolase inhibitor, propranolol, suppressed generation of diacylglycerol as it potentiated the accumulation of phosphatidic acid in F--treated neutrophils. This effect was observed both in the presence and absence of extracellular Ca2+. Moreover, high levels of propranolol (160μmol/L) effected complete inhibition of diacylglycerol generation in F--treated neutrophils with a corresponding increase in phosphatidic acid generation. Phosphatidylethanol accumulated in neutrophils stimulated with F- in the presence of ethanol. The extent of phosphatidylethanol accumulation at all time points after addition of F- corresponded to decreased levels of both phosphatidic acid and diacylglycerol, indicating that phosphatidylethanol was derived from the phospholipase D-catalysed transphosphatidylation reaction. The results indicate that F- activates a Ca2+-independant phospholipase D, which appears to be the major, if not sole, catalyst for both phosphatidic acid and diacylglycerol generation in F--treated neutrophils. Ca2+, mobilized as a result of F- stimulation and possibly as a consequence of phospholipase D activation, exerts a profound effect on cellular second messenger levels by modulating the conversion of phosphatidic acid to diacylglycerol.

Key words: Diacylglycerol; Fluoride-treated; Neutrophils; Phospholipase D.
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SODIUM FLUORIDE INFLUENCE UPON ENERGY AND PROTEIN LIVER METABOLISM AFTER ITS EXPERIMENTAL ISCHEMIA

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Abstract from Fiziologicheskii Zhurnal 38 (1) 42-6 1992

The experimental study of 88 white rats has stated that peroral introduction of sodium fluoride at a rate of 1.2 mg per 100 g of mass in animals during 3 month period is followed by the development of fluoride intoxication, that causes a considerable decrease of liver resistance to ishemia and more vivid disturbances of its energy and protein metabolism. The activity of the restoration plastic processes after ishemia decreases. A conclusion is drawn that fluoride can influence the seriousness of illness, ishemia undelying it.

Key words: Sodium fluoride; Liver metabolism; Ischemia
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MULTIPLE ACTIONS OF FLUORIDE IONS UPON THE PHOSPHOINOSITIDE CYCLE IN THE RAT BRAIN

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Abstract from: Brain Research, 573 93-101 1990

The effects of sodium fluoride upon basal and agonist-stimulated inositol phospholipid breakdown have been investigated in rat brain miniprisms. NaF concentration independently increased basal inositol phospholipid breakdown, with a maximum effect being seen at 20 mM. NaF reduced the inositol phospholipid breakdown responses to stimulation by carbachol, noradrenaline, serotonin and quisqualate, but not to the stimulation produced by raising the assay (K+) from 6 to 18 mM. More detailed study demonstrated NaF to have a 'leveling' effect, reducing all InsP/(Lipid+InsP) values > 0.15 (i.e. produced by carbachol at raised [K+], noradrenaline and by 50 mM K+) to about this value. Time-course experiments indicated that NaF treatment reduced the rate of carbachol-stimulated inositolphospholipid breakdown up to this InsP/(Lipid + InsP) level and thereafter blocked further breakdown. Inhibitory effects upon carbachol-stimulated inositol phospholipid breakdown were not seen with forskolin, sodium nitroprusside or 8BrcGMP. Under conditions where there is no de nova synthesis of phosphoinositides from [3H]myo-inositol, NaF reduced the total Lipid+InsP labelling by about 20%. NaF in addition inhibits the activity of Ins(1,4)P_2-phosphatase in cerebral cortical homogenates. It is concluded that fluoride ions inhibit agonist-stimulated inositol phospholipid breakdown via actions not only on G-proteins but also on phosphoinositide-specific phospholipase C substrate availability.

Key words: Fluoride ion; G-protein; Muscarinic receptor; Polyphosphoinositide metabolism; Rat brain.
Reprints: C J Fowler, Astra Research Centre AB, S-151 85 Södertälje, Sweden.
FLUORIDE, CALCIUM AND PHOSPHORUS METABOLISM IN THE RAT:
COMPARISON OF 'NATURAL INGREDIENT' WITH SEMIPURIFIED DIETS

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Three groups of weanling female rats were fed different, commercial available, 'natural ingredient' diets containing 12, 28 or 45 parts/10^6 F, mainly as bone meal, for six weeks. Two other groups were fed a low-fluoride (0.76 parts/10^6) semipurified diet. They received fluoride doses, either in the drinking water or by daily intraperitoneal injection, which were approximately equal to the average dose of the other three groups. Rats on the 'natural ingredient' diets ingested more food and water and excreted more faeces and urine, effects which were attributed to the higher amounts of dietary fibre, Na, K and Cl. Thus, at any given concentration of fluoride in the food or water, the level of fluoride ingestion and the ensuing effects would be influenced by the type of diet used. The values for fractional fluoride absorption (45-49%) and retention (38-47%) were similar among the groups given 'natural ingredient' diets. In the groups given semipurified diet, the corresponding values were about twice as high with the exception that fractional absorption was negative (-41%) in the injected group, which indicated net intestinal secretion of fluoride. Fluoride balances and tissue concentrations were highest in the groups fed the semipurified diet, even though the level of intake was not always higher. The fractional values for calcium and phosphorus absorption (41-51%) and retention (33-43%) were also similar among the groups given 'natural ingredient' diets. The corresponding values were about twice as high in the groups fed the semipurified diet. In terms of supporting maximum bone calcification, phosphorus absorption was marginal in two of the groups on the 'natural ingredient' diets. Because of their variable fluoride concentrations and ill-defined compositions, the use of 'natural ingredient' diets in research should be avoided.

Key words: Absorption; Balance; Bone fluoride; Bone mineralization; cAMP;
Dental fluorosis; Enamel fluoride; Enamel mineralization; Faecal excretion; Intake;
Osteoporosis; Plasma fluoride; Retention; Urinary excretion.

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A COMPARITIVE STUDY OF FLUORIDE PHARMACOKINETICS IN FIVE SPECIES

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Abstract from: Journal of Dental Research 70 (6) 948-51 1991

This study was designed to quantitate and compare the major features of the short-term pharmacokinetics of fluoride - i.e., the plasma (Cp), renal (Cr), and extra-renal (Cer) clearances - in young adult dogs, cats, rabbits, rats, and hamsters. Plasma and urine samples were collected for seven h after the iv administration of fluoride (0.5 mg F/kg). Cp ranged from 3.5 to 8.6 mL/min/kg in the dog and hamster, respectively. Cr ranged from less than 1.5 mL/min/kg in the dog and rabbit to about 3.5 mL/min/kg in the rat and hamster. Cer ranged from 2.1 mL/min/kg in the dog to over 4.5 mL/min/kg in the cat,
rabbit, and hamster. It was concluded that 1) there are major quantitative differences in the metabolic handling of fluoride among the five species, and that 2) Cp, Cr, and Cer values of the young adult dog, when factored for body weight, resemble those of the young adult human most closely.

Key words: Cats; Dogs; Fluoride pharmacokinetics; Hamsters; Rabbits; Rats.
Reprints: G M Whitford, Department of Oral Biology, Medical College of Georgia, Augusta GA 30912-1129 USA.

THE EFFECT OF CALCIUM ON DISODIUM MONOFLUOROPHOSPHATE ABSORPTION FROM THE GASTROINTESTINAL TRACT OF RATS
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The absorption of fluoride from disodium monofluorophosphate with or without added calcium has been studied in ligated stomachs and duodena of rats, in vivo. Measurements of fluoride absorption from sodium fluoride were also carried out for comparative purposes. The formation constant of the soluble, neutral calcium monofluorophosphate 0 complex has been determined at 20-degrees, 25-degrees and 37-degrees-C. Its value at 37-degrees-C being 315 +/- 10(molar units). The influence of increasing concentrations of calcium on alkaline phosphatase (E.C.3.1.3.1) activity whith disodium 0 monofluorophosphate as substrate has been also studied. Gastric absorption of 2mM disodium monofluorophosphate in the presence of 50mM calcium was much slower than that of 2mM disodium monofluorophosphate alone. The latter was slower than that of 2mM sodium fluoride. The opposite situation has been found for the duodenal fluoride absorption. Results obtained are interpreted in terms of the occurrence of an intestinal monofluorophosphate hydrolysis prior to its absorption as fluoride. In addition, data presented suggest an independent and parallel pathway of fluoride absorption in the form of the liposoluble calcium monofluorophosphate complex.

Key words: Calcium; Disodium monofluorophosphate; Gastrointestinal tract; Rats.
Reprints: A Villa, University of Chile, Inta, Unidad Bioquim Farmacol & Lipidos, Casilla 138-11, Santiago, Chile.

INHIBITION OF PROTON-TRANSLOCATING ATPASES OF STREPTOCOCCUS MUTANS AND LACTOBACILLUS CASEI BY FLUORIDE AND ALUMINUM
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One of the major effects of fluoride on oral bacteria is a reduction in acid tolerance, and presumably also in cariogenicity. The reduction appears to involve transport of protons across the cell membrane by the weak acid HF to dissipate the pH gradient, and also direct inhibition of the F,Fo, proton-translocating ATPases of the organisms, especially for Streptococcus mutans. This direct inhibition by fluoride was found to be dependent on aluminum. The dependence on aluminum was indicated by the protection against fluoride inhibition afforded by the Al-chelator deferoxamine and by loss of protection after addition of umolar levels of Al^3+, which were not inhibitory for the enzyme in the absence of fluoride. The F,F form of the enzyme dissociated from the cell membrane previously had
been found to be resistant to fluoride in comparison with the $F_1F_0$ membrane-associated form. However, this difference appeared to depend on less aluminum in the $F_1$ preparation in that the sensitivity of the $F_1$ enzyme to fluoride could be increased by addition of umolar levels of $Al^{3+}$. The effects of $Al$ on fluoride inhibition were apparent when enzyme activity was assayed in terms of phosphate release from ATP or with an ATP-regenerating system containing phosphoenolpyruvate, pyruvate kinase, NADH and lactic dehydrogenase. Also, $Be^{2+}$ but not other metal cations, e.g. $Co^{2+}, Fe^{2+}, Fe^{3+}, Mn^{2+}, Sn^{2+},$ and $Zn^{2+}$, served to sensitize the enzyme to fluoride inhibition. The differences in sensitivities of enzymes isolated from various oral bacteria found previously also appeared to be related to differences in levels of $Al$. Even the fluoride-resistant enzyme of isolated membranes of *Lactobacillus casei* ATCC 4646 could be rendered fluoride-sensitive through addition of $Al^{3+}$. Thus, the $F_1F_0$ ATPases of oral bacteria were similar to $E_1E_0$ ATPases of eukaryotes in being inhibited by $Al$-F complexes, and the inhibition presumably involved formation of ADP-$Al$-$F_2^-$ complexes during catalysis at the active side of the enzymes.

Key words: Aluminum; $F_1F_0$ ATPase; Fluoride; *Lactobacillus casei*; Oral bacteria; 

Streptococcus mutans.

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ALUMINUM STIMULATES THE PROLIFERATION AND DIFFERENTIATION OF OSTEOBLASTS IN VITRO BY A MECHANISM THAT IS DIFFERENT FROM FLUORIDE

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Abstract from *Molecular and Cellular Biochemistry* 105 93-105 1991

Micromolar concentrations of aluminum sulfate consistently stimulated [3H]thymidine incorporation into DNA and increased cellular alkaline phosphatase activity (an osteoblastic differentiation marker) in osteoblast-line cells of chicken and human. The stimulations were highly reproducible, and were byphasic and dose-dependent with the maximal stimulatory dose varied from experiment to experiment. The mitogenic doses of aluminum ion also stimulated collagen synthesis in cultured human osteosarcoma TE-85 cells, suggesting that aluminum ion might stimulate bone formation in vitro. The effects of mitogenic doses of aluminum ion on basal osteocalcin by normal human osteoblasts could not be determined since there was little, if any, basal secretion of osteocalcin by these cells. 1,25 Dihydroxyvitamin $D_3$ significantly stimulated the secretion of osteocalcin and the specific activity of cellular alkaline phosphatase in the human osteoblasts. Although mitogenic concentrations of aluminum ion potentiated the 1,25 dihydroxy-vitamin $D_3$-dependent stimulation of osteocalcin secretion, they significantly inhibited the hormone-mediated activation of cellular alkaline phosphatase activity. Mitogenic concentrations of aluminum ion did not stimulate cAMP production in human osteosarcoma TE85 cells, indicating that the mechanism of aluminum ion does not involve cAMP. The mitogenic activity of aluminum ion is different from that of fluoride because (a) unlike fluoride, its mitogenic activity was unaffected by culture medium changes; (b) unlike fluoride, its mitogenic activity was nonspecific for bone cells; and (c) aluminum ion interacted with
fluoride on the stimulation of the proliferation of osteoblastic-line of cells, and did not share the same rate-limiting step(s) as that of fluoride. PTH interacted with and potentiated the bone cell mitogenic activity of aluminum ion, and thereby is consistent with the possibility that the \textit{in vivo} osteogenic actions of aluminum ion, might depend on PTH. In summary, low concentrations of aluminum ion could act directly on osteoblasts to stimulate their proliferation and differentiation by a mechanism that is different from fluoride.

Key words: Aluminum; Bone formation; Differentiation; Fluoride; Osteoblasts; Proliferation.

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EFFECT OF FLUORIDE ON BONE AND BONE CELLS IN OVARIECTOMIZED RATS
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Abstract from \textit{Journal of Bone and Mineral Research} 7 (8) 961-9, 1992

To evaluate whether treatment with a mitogenic agent may increase bone formation and bone mass in osteopenia induced by estrogen deficiency, we determined the effect of oral fluoride treatment on bone and bone cells in ovariectomized rats. Sodium fluoride (NaF) was administered to 3-month-old ovariectomized rats 1 day after ovariectomy (OVX) for 1, 3, and 6 months. NaF was given in drinking water at the dose of 1 mg/kg body weight per day. Fluoride administration led to a partial prevention of the bone loss induced by OVX as shown by histologic analysis of tibial metaphysis and by evaluation of femoral calcium content. These beneficial effects of fluoride were more striking at early time points (1 and 3 months postovariectomy) than after 6 months of treatment. The increase in trabecular bone volume in OVX rats treated with fluoride was associated with a rise in the osteoblast surface, which was increased by 60, 72, and 235% at 1, 3, and 6 months postovariectomy compared to untreated OVX rats. In OVX rats and in sham-operated rats plasma osteocalcin was increased in correlation with the osteoblast surface. However, these two parameters were not correlated in OVX rats treated with fluoride. The heat-labile bone-specific alkaline phosphatase in plasma was decreased in OVX rats treated with fluoride compared to OVX rats, suggesting that both the number and the activity of osteoblasts were affected by NaF treatment. To examine the effect of fluoride on the osteocalcin production and the proliferative capacity of bone cells, osteoblastic cells were isolated by collagenase digestion from the bone surface of tibia in treated and untreated OVX rats. In OVX rats DNA synthesis by cultured bone cells was markedly increased compared to sham rats. In OVX rats treated with fluoride DNA synthesis tended to be further increased compared to untreated OVX rats as evaluated by thymidine incorporation into DNA. Osteocalcin production by osteoblastic cells in vitro was comparable in the different groups. The results of this study show that oral treatment with fluoride partially prevents the bone loss induced by estrogen deficiency in OVX rats. This beneficial effect of fluoride results from a further stimulation of bone formation as shown in vivo by an increased extent of bone-forming cells and in vitro by an enhancement of the proliferative capacity of osteoblastic cells isolated from the bone surface.

Key words: Bone; Bone cells; Estrogen deficiency; Fluoride; Ovariectomy; Rats.

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INCORPORATION OF SODIUM FLUORIDE INTO CORTICAL BONE DOES NOT IMPAIR THE MECHANICAL PROPERTIES OF THE APPENDICULAR SKELETON IN RATS

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Abstract from Calcified Tissue International 51 (2) 127-31 1992

Clinical studies on the use of sodium fluoride (NaF) in osteoporotic patients have demonstrated increased spinal bone mass without a reduction in vertebral fracture incidence, and a trend towards reduced appendicular bone mass with an increase in peripheral fracture incidence. As previous reports have suggested that NaF becomes incorporated into bone's crystal structure, possibly affecting bone strength, we sought to examine the relationship among bone fluoride content, bone mass, and skeletal fragility. Twenty-one-day-old female Sprague-Dawley rats were treated with four different doses of NaF. The tibiae were subjected to histomorphometric and biochemical analyses, and the femora were tested in torsion for the properties of strength, stiffness, energy storage capacity, and angular deformation. The results showed that over 50% of the skeleton in these rats was turned over in the presence of NaF. The four different doses resulted in a linear increase in bone F concentration and suggested excellent absorption and incorporation of this drug. No changes in histomorphometric indices of bone formation or turnover were found. Despite the large fraction of bone formed during NaF treatment, and the linear increase in bone fluoride content in relation to dose, there were no changes observed in any of the mechanical properties. These results suggest that, even extensive incorporation of fluoride into bone, in the absence of an effect on bone mass or remodeling, does not significantly alter its capacity to withstand mechanical loads.

Key words: Sodium fluoride; Cortical bone; Mechanical properties; Histomorphometry; Bone mass.

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A HISTOMORPHOMETRIC ANALYSIS OF THE EFFECTS OF FLUORIDE ON EXPERIMENTAL ECTOPIC BONE FORMATION IN THE RAT

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Abstract from Journal of Dental Research 70 (6) 957-60 1991

Ectopic bone formation was induced in 14 rats receiving 100 ppm fluoride in drinking water and in 14 control animals. Sections from ossicles removed after 14 and 20 days were sampled for stereological analysis. Bone volume density and bone volume were reduced in experimental animals on day 14 (p <0.05). This difference was no longer present after 20 days. On day 20, surface density and areas of formative surfaces were increased in the fluoride group (p <0.05). Osteoid seam thickness was higher in the fluoride group on both days (p <0.01). In conclusion, fluoride induced quantitative alterations in ectopic bone formation, and the presented model may prove a useful addendum to previous methods for investigation of fluoride effects on mineralization processes in vivo.

Key words: Ectopic bone formation; Fluoride; Histomorphometric analysis; Rats.

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THE EFFECTS OF FLUORIDE ON BONE
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Abstract from: Clinical Orthopaedics and Related Research 267 264-7 1991

Fluoride has often been used as a treatment for osteoporosis, a metabolic bone disease of considerable importance in the elderly population. The techniques currently used to monitor a patient’s response to fluoride are outlined. New findings concerning 1) a mechanism for interaction of fluoride with osteoblasts (via mitogenic signals or growth factors); 2) toxicity and carcinogenesis; (3) recent clinical trial data; and 4) the importance of dosage, administration regimens, and side effects in an effective fluoride treatment protocol are reviewed. Some recent clinical data challenge the efficacy of fluoride in the treatment of postmenopausal osteoporosis. Because of the implications of these recent studies with respect to fracture incidence during fluoride therapy, fluoride cannot be recommended at this time for general use in the treatment of osteoporosis.

Key words: Bone; Fluoride; Osteoporosis.
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FLUORIDE THERAPY FOR OSTEOPOROSIS: A REVIEW OF DOSE RESPONSE, DURATION OF TREATMENT, AND SKELETAL SITES IN ACTION
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Abstract from Calcified Tissue International 49(Suppl) S64-7 1991

Osteoporosis is a disease characterized by a reduction in bone density which predisposes to fracture after even minimal trauma. Fluoride, because it has consistently been shown to stimulate bone formation and increase trabecular bone density, has been widely studied for the treatment of osteoporosis. The article focuses on the dose response, duration of treatment, and skeletal sites of action of fluoride; we also include comments on the effect of fluoride on vertebral and appendicular fracture rates. The skeletal response to fluoride doses, ranging from 15 to 43 mg elemental fluoride per day, included a linear increase in spinal bone density at an average rate of $1.25 \pm 0.91$ mg/cm$^3$ per month. The rate of increase in spinal bone density was related to the dose of fluoride ($r = 0.34$, $P < 0.03$). Spinal bone density had increased above the fracture threshold in 44% of patients treated with fluoride for $32 \pm 10$ months. The time required to achieve this goal was, however, influenced by the pre-treatment spinal bone density and interpatient variation in response to fluoride treatment. Patients whose spinal bone density remained below the fracture threshold had lower pretreatment bone densities and/or slower rates of increase in spinal bone density ($P < 0.001$). The osteogenic effect of fluoride was not limited to the spine. After 2 years of fluoride therapy, we found bone density in the femoral condyle (measured by QCT) to have increased by $13 \pm 2.5$ mg/cm$^3$ ($n = 38$, $P < 0.001$); bone density in the hip (measured by DPA) was increased by $0.0261 \pm 0.015$ g/cm$^2$ ($n = 55$, $P < 0.025$). The efficacy of fluoride therapy to reduce fractures is not well established. Recently, investigators from the Mayo Clinic and Henry Ford Hospital reported fluoride had no effect on the vertebral fracture rate despite a significant increase in spinal bone density, but this finding has not been supported by findings in other studies. Moreover, our preliminary analysis of over 500 fluoride-treated patients found a time-dependant decrease in vertebral fracture rate related to a corresponding increase in spinal bone density. We conclude that these data, together with the many other positive

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international findings related to fluoride, justify continued investigation of this potent agent for the treatment of osteoporosis.

Key words: Fluorides; Osteoporosis.
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IS FLUORIDE TREATMENT JUSTIFIED TODAY?
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Abstract from Calcified Tissue International 49 (suppl) 568-9 1991

Fluoride has been used for the treatment of osteoporosis since 1961, because it increases trabecular bone mass in the spine and may be effective in the treatment of spinal osteoporosis. Fluoride treatment is still controversial because of its side effects, the high rate of non-responders, possible osteomalacic effect on bone, deleterious effects on cortical bone, and especially because of its uncertain effect on fracture rate. At present, fluoride therapy is highly questionable in the prophylaxis and treatment of osteoporosis.

Key words: Fluoride; Osteoporosis.
Reprints: J A Inkovaara, University Central Hospital, 33520 Tampere, Finland

DOSE EFFECTS ON EWE BONE REMODELING OF SHORT-TERM SODIUM FLUORIDE ADMINISTRATION: A HISTOMORPHOMETRIC AND BIOCHEMICAL STUDY

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Abstract from Bone 12: (6) 421-7 1991

The early effects of two doses of sodium fluoride (NaF) on bone remodeling were studied in 14 ewes divided into two groups. Group I received orally 1 mg NaF/kg/day and group II received a five-fold greater dose. No calcium supplement was given. Transiliac bone biopsies and blood samples were taken before treatment (T0) and after 45 (T45) days of treatment. Bone fluoride content significantly increased in group II. In both groups, a significant decrease of serum calcium and phosphorus, and a slight but nonsignificant augmentation in serum parathyroid hormone were noted. Osteoid perimeter and area were significantly increased. The osteoid width significantly increased in both groups, but was twice higher in group II than I. At T45, the osteoblast perimeter increased in both groups. Osteoid perimeter was significantly correlated with serum osteocalcin values ($r = 0.74$, $p < 0.001$) and bone fluoride content ($r = 0.64$; $p < 0.01$). The bone formation rate at tissue level tended to increase in both groups. Concerning the apposition rate, a decrease was noted which was 1.5-fold higher in group II than in I. The increased formation period resulted from a prolonged inactive period in group II. These results point out a stimulatory effect of fluoride on the birth rate of osteoblasts. However, fluoride prolonged the lifespan of osteoblasts that had reduced activity.

Key words: Biochemical investigations; Bone remodeling; Dose; Ewe; Histomorphometry; Sodium fluoride
Reprints: P Chavassieux MD, INSERM Unité 234, Faculté Alexis Carrel, Rue G Paradin, 69372 Lyons Cedex 08, France
FLUORIDE-INDUCED BONE CHANGES IN LAMBS DURING AND AFTER EXPOSURE TO SODIUM FLUORIDE

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Abstract from Osteoporosis International 2 26-33 1991

The evolution of bone changes induced by fluoride after the end of exposure was investigated in lambs. Sodium fluoride (NaF) was given orally at a dose of 3.5mg/kg per day to 14 animals for 120 days. A group of 7 controls and 7 treated lambs was slaughtered at the end of NaF administration (T120) and another group 120 days after the end of NaF exposure (T240). At T120, the bone fluoride content (BFC) was very significantly increased in treated animals. The histomorphometric analysis confirmed that fluoride induces an increase in bone formation (the osteoid perimeter and area were 3-fold and 4.5-fold higher respectively in treated than in control animals). The number of osteoblasts was significantly augmented. Serum osteocalcin level was twice as high in treated animals compared with controls. The bone formation rate at the tissue level (BFR) doubled after treatment, but the apposition rate (Aj.AR) was half that in the control group. The mineralization lag time (Mit) was 120 days in treated animals compared with 42 days in controls. At T240, BFC had decreased by 50% compared with the level at T120, but it was still significantly higher than in controls. The osteoid and osteoblastic parameters were 2 and 1.3 times higher than in control animals. BFR remained significantly increased in treated animals, but Aj.AR and Mit were similar in control and treated animals. In conclusion, after 4 months of NaF exposure, positive effects on bone formation were still present but the evidence of cellular toxicity had disappeared.

Key words: Bone fluoride content; Bone remodeling; Fluoride; Histomorphometry; Lambs.

STUDIES OF FLUORIDE RETENTION BY ORAL SOFT TISSUES AFTER THE APPLICATION OF HOME-USE TOPICAL FLUORIDES

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Abstract from Journal of Dental Research 71 (9) 1546-52 1992

Previous studies have focused on enamel and plaque as the primary sites of fluoride (F) retention in the mouth. The present study was undertaken to evaluate the role of oral soft tissue as a site of F retention by comparing an edentulous subject panel (n = 9) with a fully dentate panel (n = 10). Unstimulated whole saliva samples were collected by having subjects pool saliva for two min. Samples were collected over a 24-hour period after application of a placebo dentifrice (PD; 0.4 ppm F), fluoride dentifrice (FD; 1 100 ppm F), fluoride rinse (FR; 226 ppm F), or fluoride gel (FG; 5000 ppm F) delivered in custom trays. There was no statistically significant difference in salivary flow rate between the two panels for any of the treatments. The edentulous panel had higher salivary F levels than the dentate panel, but reached statistical significance (p < 0.05) for the FD and FG treatments. In a separate study involving the same treatments, F levels at specific soft-tissue sites were measured over a one-hour period by use of absorbent discs placed in
different soft-tissue areas of the mouth. The tongue and lower posterior vestibule retained the highest F levels, followed by the upper posterior buccal vestibule and upper anterior labial vestibule, with the lowest F levels retained in the lower anterior vestibule and the floor of the mouth. There was a strong-to-moderate correlation between whole saliva F concentration and F levels at specific soft-tissue sites. This study establishes the importance of oral soft tissue as the major site of F retention in the mouth.

Key words: Fluoride retention; Oral soft tissues; Topical fluorides.
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EFFECTS OF FLUORIDE ON SECRETORY AND POSTSECRETORY PHASES OF ENAMEL FORMATION IN SHEEP MOLARS

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Abstract from American Journal of Veterinary Research 53 (7) 1241-7 1992

Effect of fluoride was assessed on molars during and after mineralization. Two groups of 7 sheep each were dosed orally with 3.5mg of fluoride/kg of body weight daily for 4 months (from 5 to 9 months after birth). Sheep of the first group were slaughtered immediately after fluoride administration; those of the second group were slaughtered 4 months later at the age of 13 months. Three control groups of 7 sheep each were slaughtered at 5 months (to determine the state of the teeth at the beginning of fluoride administration), and at 9 and 13 months.

During fluoride administration, plasma fluoride concentration rapidly increased to about 0.50 µg/ml; after fluoride administration, it stabilized at 0.20 µg/ml in treated sheep, whereas controls had concentration of 0.10 µg/ml (P<0.01).

Parts of the molars that were in the process of mineralization during fluoride administration (mainly second molars) had thinning enamel, with pits, mainly close to the apex, marked decrease in hardness throughout the layer (< 100 Vickers U, compared with 240 Vickers U), and fluoride accumulation twice as high as that in controls. (1,000 to 2,500 mg/kg [dry weight]). Fluoride accumulation was higher in dentine (2,700 to 4,200 mg/kg), but hardness was less affected.

On parts of the molars that were already mineralized (mostly, the first molar), changes in the appearance of the enamel and cementum, decreased hardness (less important than in teeth during mineralization) affecting outer enamel more than inner enamel, high fluoride concentration (4,000 to 5,500 mg/kg [dry weight]) in outer enamel extending over 200 µm were observed. Thus, in sheep, fluoride has a substantial post-secretory effect that may be explained by a slower maturation phase of enamel in this species.

Because molar wear is correlated to enamel hardness (dentine at the occlusal surface has low resistance - 30 Vickers U), abnormal abrasion of molar teeth that have mineralized before and during fluoride intakes can be observed.

Key words: Fluoride; Enamel formation; Sheep molars.
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INFLUENCE OF FLUORIDE AND CARBONATE ON IN VITRO REMINERALIZATION OF BOVINE ENAMEL

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The influence of fluoride, carbonate, and fluoride in combination with carbonate on the in vitro remineralization of bovine enamel was investigated with the use of a sandwich technique. After demineralization, enamel slices were subjected for 610 h to remineralizing solutions with 0.03 or 1.0 ppm fluoride. At each fluoride level, either 0, 1, 10, 20, or 25 mmol/L carbonate was tested. After 0, 22, 62, 126, 192, 329, and 610 h of remineralization, contact microradiographs were made by Cu Kα-radiation. At 0.03 ppm fluoride, carbonate had an inhibiting influence on remineralization. At 1.0 ppm fluoride, the inhibiting influence of carbonate changed into a stimulation of remineralization at 20 and 25 mmol/L carbonate. At 0, 1, and 10 mmol/L carbonate, fluoride had an inhibiting influence on remineralization. The differences in remineralization between the groups were explained by events concerning crystal growth, i.e., different types of minerals might have precipitated with differences in precipitation rates, and retardation of a precipitation step might have occurred under the various remineralization conditions. There was a mutual influence of fluoride and carbonate on the remineralization process. We conclude that the composition of the remineralizing solution with respect to fluoride and carbonate concentrations is important for the remineralization process.

Key words: Carbonate; Fluoride; Remineralization.

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BENEFITS AND RISKS OF FLUORIDE SUPPLEMENTATION: CARIES PREVENTION VERSUS DENTAL FLUOROSIS

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To assess the risks (dental fluorosis) and the benefits (caries prevention) of fluoride (F) tablets and F toothpaste, we surveyed 2003 schoolchildren aged 5-20 years old (mean = 10.82, SD = 3.40). Children were scored for dental caries by means of the decayed, missing, filled teeth index (DMFT index). Frequent use of F toothpaste (toothbrushing frequency) is poorly linked to caries (Spearman r = 0.05, P = 0.02) and dental fluorosis (r = 0.05, P = 0.03). Children who use F tablets regularly and appropriately exhibit mild fluorosis more often than non- or occasional users (odds ratio = 9.58), and have a mean DMFT index 50% lower than other children. We conclude that using F tablets is an effective means of preventing caries. When used appropriately in non fluoridated areas, using F tablets results in minor damage.

Key Words: Caries; Caries prevention; Dental fluorosis, Fluoride.

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