

ABSTRACTS

DENTAL EFFECTS

OUTCOMES ASSOCIATED WITH DENTISTS' RISK ASSESSMENT

OBJECTIVE: To examine retrospectively the caries-related restorative experience of at-risk individuals who received fluoride-based preventive interventions to determine if the intervention resulted in fewer caries-related procedures. **METHODS:** Administrative data from two dental health plans were used to determine the relationship between caries risk assessment (CRA) scores, preventive treatment and caries-related treatment procedures. We identified 45,693 adults who were consecutively enrolled for at least 1 year before and 2.5 years after the CRA. Variables representing the number of teeth with any caries-related treatment procedure and receipt of preventive treatment were created. **RESULTS:** The outcome variable of interest was having at least one tooth with a caries-related procedure in the 2-year follow-up period. In plan A, the recommendation for home-use fluoride was not significantly related to caries-related treatment procedures in the follow-up period for individuals at low, moderate or high risk ($P>0.300$). In plan B, application of in-office fluoride was associated with having at least one tooth with a caries-related treatment procedure in the follow-up period ($P<0.001$). **CONCLUSIONS:** We found incomplete compliance with guidelines for recommendation or administration of preventive treatment for patients at elevated risk for caries. We were also unable to identify any significant reductions in caries-related procedures for individuals receiving a fluoride intervention, compared with those who did not, when stratified by risk level.

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Keywords: Caries-related treatment; Caries risk assessment; Home-use fluoride; In-office fluoride; Preventive treatment.

Source: Community Dent Oral Epidemiol 2006 Oct;34(5):381-6.

HEALTH/BIOLOGICAL EFFECTS IN HUMANS

FLUOROTOXIC METABOLIC BONE DISEASE: AN OSTEO-RENAL SYNDROME CAUSED BY EXCESS FLUORIDE INGESTION IN THE TROPICS

BACKGROUND: There is scant data available on the pathogenetic mechanisms of varied clinical presentation of bone disease in patients with excess fluoride ingestion in the Indian subcontinent. The present study is comprehensive and state of the art, incorporating all essential elements of bone mineral metabolism in patients with excess fluoride ingestion. **METHODS:** We studied 24 patients (age 31 ± 16 years) with fluorotoxic metabolic bone disease (FMBD) for their clinical, radiological, and biochemical parameters like serum calcium, phosphorus, alkaline phosphatase (SAP), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and parathyroid hormone levels, as well as nephrologic parameters that assess renal handling of calcium and phosphorus and skeletal dynamics as revealed by bone histomorphometry. **FINDINGS:** Major clinical manifestations were bone pain (79%), tetany (12.5%), and dental mottling (38%). Radiological findings included osteosclerosis (96%), pseudofracture, and ligamentous calcification (50%). These patients manifested hypocalcemia and raised SAP with normal serum phosphorus. There was a positive correlation between serum creatinine and phosphorus excretion index (PEI) and a negative correlation between declining endogenous creatinine clearance (CreCl) and increasing renal loss of calcium and phosphorus as indicated by increased calcium-to-creatinine ratio and PEI. Bone histomorphometry revealed impairment of primary mineralization with hypomineralized lacunae, interstitial mineralization defects, and very thick and extended osteoid seams. Autopsy findings in a patient who died of azotemia showed tubular atrophy with secondary glomerular changes. **INTERPRETATION:** Fluoride intoxication plays an important role in the

pathogenesis of the unique osteo-renal syndrome.

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Keywords: Alkaline phosphatase; Bone disease; Bone histomorphology; Calcium; Creatinine; Dihydroxyvitamin D; Fluoride ingestion; Glomerular changes; Hypocalcemia; Ligamentous calcification; Osteo-renal syndrome; Osteosclerosis; Mineralization; Parathyroid hormone; Phosphorus; Pseudofracture; Tetany.

Source: Bone 2006 Oct;39(4):907-14.

SEVERE BONE DEFORMITIES IN YOUNG CHILDREN FROM VITAMIN D DEFICIENCY AND FLUOROSIS IN BIHAR-INDIA

A case-control study was undertaken to understand the etiopathology of the bone deformities among young children in a fluoride-affected village of the Bihar State. Two villages were selected: one village with high fluoride in drinking water (7.9 ± 4.15 ppm), and the other village with normal levels of fluoride (0.6 ± 0.31 ppm) as the control village. In both villages bore wells were the source of drinking water. Two hundred and forty subjects from 54 households (HHs) of the high-fluoride village (HFV) and 1443 subjects from 197 HHs of the control village were selected for the study. Dental mottling (DM) was observed in 50% and skeletal deformities of various forms were observed in 20% of the total population of HFV, whereas, in the control village, the incidence of DM was 6% and skeletal deformities were absent. The prevalence of both DM and skeletal deformities was high in the younger age group of 1.5 to 14 years. Genu valgum, genu varum, bowing of tibia, saber shin, and widening of the lower ends of long bones at the wrist were the typical skeletal deformities observed among affected children in the HFV. X-rays of the children with deformities revealed varying degrees of bending of bones and enlargement of epiphyseal ends of metaphyses with fraying of bone and ligamental calcification. A survey indicated significantly low calcium and high phosphorus intake among the population of the HFV as compared to that of the control village, possibly resulting from low intake of milk and high intake of potatoes, respectively. The mean urinary fluoride level was significantly higher in the children of the HFV, both with and without deformities, as compared to that of the control village. The mean serum 25-hydroxyvitamin D3 and calcium levels were significantly lower, and alkaline phosphatase activity was significantly higher among the children with deformities as compared to those without deformities from the HFV and the control village. Serum intact parathyroid hormone (IPTH) levels were high in children both with and without deformities in the HFV village as compared to those in the control village. No significant differences were observed in the concentration of serum and urinary creatinine, Cu, and Mg levels between the HFV and the control village. It can be concluded that some of the children from the HFV village manifested severe bone deformities (rickets), which were confirmed by the existence of low serum calcium and vitamin D levels.

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Keywords: Alkaline phosphatase; Bihar, India; Bone deformities; Calcium; Dental fluorosis; Fluorosis; Genu valgum; Genu varum; Parathyroid hormone; Rickets; Skeletal fluorosis; Creatinine; Vitamin D deficiency; Young children.

Source: Calcif Tissue Int 2005 Jun;76(6):412-8.

Editorial note: The inclusion of the following abstract remedies its omission from *Fluoride* at the time of its publication in 1998. We apologize to our readers for the delay in reporting on this valuable review.

ENDEMIC CHRONIC FLUORIDE TOXICITY AND DIETARY CALCIUM DEFICIENCY INTERACTION SYNDROMES OF METABOLIC BONE DISEASE AND DEFORMITIES IN INDIA: YEAR 2000

Epidemiological studies during 1963-1997 were conducted in 45,725 children exposed to

high intake of endemic fluoride in the drinking water since their birth. Children with adequate (dietary calcium >800 mg/d) and inadequate (dietary calcium < 300 mg/d) calcium nutrition and with comparable intakes of fluoride (mean 9.5±1.9mg/d) were compared. The toxic-effects of fluoride were severe and more complex and the incidence of metabolic bone disease (rickets, osteoporosis, PTH bone disease) and bony leg deformities (genu valgum, genu varum, bowing, rotational and wind-swept) was greater(> 90%) in children with calcium deficiency as compared to < 25% in children with adequate calcium who largely had osteosclerotic form of skeletal fluorosis with minimal secondary hyperparathyroidism. The syndrome of skeletal fluorosis and associated metabolic bone disease and deformity is a unique clinical entity classified as a variant of osteosclerotic form of skeletal fluorosis. This syndrome chiefly results from the biological impact of excess fluoride, low calcium, high PTH and 1,25-(OH)₂D₃ separately and through their interactions on bone structure and metabolism as studied by radiology, bone scanning, bone histomorphometry and relevant metabolic and endocrine laboratory investigations. Metabolically active and vascular bones of children accumulate fluoride at a faster and greater rate than adults (at the sites of active growth). In calcium deficient children the toxic effects of fluoride manifest even at marginally high (> 2.5 mg/d) exposures to fluoride. Fluoride toxicity also exaggerates the metabolic effects of calcium deficiency on bone. The findings strongly suggest that children with calcium deficiency rickets reported in the literature should be re-investigated for possible fluoride interactions. Deep bore drinking water supply with fluoride < 0.5 ppm and improvement of calcium nutrition provide 100% protection against the toxic effects of fluoride and are recommended as the cost effective and practical public health measures for the prevention and control of endemic fluorosis.

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Keywords: Calcium deficiency; Endocrine investigations; Fluoride toxicity; Hyperparathyroidism; Metabolic bone disease; Osteosclerosis; Skeletal fluorosis.

Source: Indian J Pediatr 1998 May-Jun;65(3):371-81.

HEALTH/TOXIC EFFECTS ON ANIMALS

THE GENETIC INFLUENCE ON BONE SUSCEPTIBILITY TO FLUORIDE

INTRODUCTION: The influence of genetic background on bone and its architecture and mechanical properties is well established. Nevertheless, to date, only a few animal studies have explored an underlying genetic basis for extrinsic factor effects, such as those of fluoride, on bone metabolism. **MATERIALS AND METHODS:** This study assessed the effect of increasing fluoride concentrations in the drinking water (0 ppm, 25 ppm, 50 ppm, 100 ppm), on the bone properties in 3 inbred mouse strains that demonstrate different susceptibilities to developing enamel fluorosis (A/J, a "susceptible" strain; 129P3/J, a "resistant" strain; and SWR/J, an "intermediate" strain). Fluoride concentrations were determined in femora and vertebral bodies. Bone mineral density was evaluating, through dual energy X-ray absorptiometry (DEXA). Finally, three-point bend testing of femora, compression testing of vertebral bodies, and femoral neck-fracture testing were performed to evaluate mechanical properties. **RESULTS:** Concordant with increasing fluoride dose were significant increases of fluoride concentration in femora and vertebral bodies in all 3 strains. However, fluoride treatment had little effect on the bone mineral densities (BMD) in the 3 strains. Mechanical testing showed, significant alterations in "bone quality" in the A/J strain, whereas, moderate alterations in "bone quality" in the SWR/J strain and no effects in the 129P3/J strain were observed. **CONCLUSION:** The results suggest that genetic factors may contribute to the variation in bone response to fluoride exposure and that fluoride might affect bone properties without altering BMD.

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Keywords: Bone architecture; Bone mineral density; Femur; Fluoride and bone; Genetic differences; Mechanical testing; Mice and bone; Vertebra.

Source: Bone. 2006 Aug 18; [Epub ahead of print].

EFFECT OF OVERDOSE FLUORIDE ON THE EXPRESSION OF ENAMELIN IN RAT MANDIBULAR INCISORS

OBJECTIVE: To observe the effect of fluoride overdose on the expression of enamelin in rat mandibular incisors. **METHODS:** Twenty Wistar rats were divided randomly into two groups. Animals were maintained in standard environment with free access to food and distilled water (control group I) or water containing 100 mg F ion/L (experimental group II). The rats were killed in the eighth week. Haematoxylin staining was used to observe the morphology of ameloblasts. Immunohistochemical staining was adopted to study the expressions of enamelin in the incisors. **RESULTS:** The ameloblasts of the F-treated rats were arranged in multi-layers. The ameloblasts in the F-group II were thinner than those in the control-group I. The expression of enamelin was disturbed in group II, and the structure of enamel matrix was in disorder. **CONCLUSION:** Fluoride overdose inhibits the secretion of enamelin and leads to abnormal development of enamel matrix.

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Keywords: Ameloblasts; Enamelin; Enamel matrix; Immunohistochemical staining; Mandibular incisor; Rats.

Source: Hua Xi Kou Qiang Yi Xue Za Zhi 2006 Aug;24(4):297-9. [article in Chinese].

NEW INSIGHTS INTO THE MECHANISM OF METHOXYFLURANE NEPHROTOXICITY AND IMPLICATIONS FOR ANESTHETIC DEVELOPMENT (PART 1): IDENTIFICATION OF THE NEPHROTOXIC METABOLIC PATHWAY

BACKGROUND: Methoxyflurane nephrotoxicity results from biotransformation; inorganic fluoride is a toxic metabolite. Concern exists about potential renal toxicity from volatile anesthetic defluorination, but many anesthetics increase fluoride concentrations without consequence. Methoxyflurane is metabolized by both dechlorination to methoxydifluoroacetic acid (MDFA, which may degrade to fluoride) and O-demethylation to fluoride and dichloroacetic acid. The metabolic pathway responsible for methoxyflurane nephrotoxicity has not, however, been identified, which was the aim of this investigation. **METHODS:** Experiments evaluated methoxyflurane metabolite formation and effects of enzyme induction or inhibition on methoxyflurane metabolism and toxicity. Rats pretreated with phenobarbital, barium sulfate, or nothing were anesthetized with methoxyflurane, and renal function and urine methoxyflurane metabolite excretion were assessed. Phenobarbital effects on MDFA metabolism and toxicity in vivo were also assessed. Metabolism of methoxyflurane and MDFA in microsomes from livers of pretreated rats was determined in vitro. **RESULTS:** Phenobarbital pretreatment increased methoxyflurane nephrotoxicity in vivo (increased diuresis and blood urea nitrogen and decreased urine osmolality) and induced in vitro hepatic microsomal methoxyflurane metabolism to inorganic fluoride (2-fold), dichloroacetic acid (1.5-fold), and MDFA (5-fold). In contrast, phenobarbital had no influence on MDFA renal effects in vivo or MDFA metabolism in vitro or in vivo. MDFA was neither metabolized to fluoride nor nephrotoxic. Barium sulfate diminished methoxyflurane metabolism and nephrotoxicity in vivo. **CONCLUSIONS:** Fluoride from methoxyflurane anesthesia derives from O-demethylation. Phenobarbital increases in methoxyflurane toxicity do not seem attributable to methoxyflurane dechlorination, MDFA toxicity, or MDFA metabolism to another toxic metabolite, suggesting that nephrotoxicity is attributable to methoxyflurane O-demethylation. Fluoride, one of many metabolites from O-demethylation,

may be toxic and/or reflect formation of a different toxic metabolite. These results may have implications for interpreting anesthetic defluorination, volatile anesthetic use, and methods to evaluate anesthetic toxicity.

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Keywords: Anesthetics; Barium sulfate; Dechlorination; Dichloroacetic acid; Diuresis; Methoxyflurane metabolism; Nephrotoxicity; O-Demethylation; Osmolality; Phenobarbital; Rats and methoxyflurane; Urinary metabolites.

Source: Anesthesiology 2006 Oct;105(4):726-36.

NEW INSIGHTS INTO THE MECHANISM OF METHOXYFLURANE NEPHROTOXICITY AND IMPLICATIONS FOR ANESTHETIC DEVELOPMENT (PART 2): IDENTIFICATION OF NEPHROTOXIC METABOLITES

BACKGROUND: Methoxyflurane nephrotoxicity results from its metabolism, which occurs by both dechlorination (to methoxydifluoroacetic acid [MDFA]) and O-demethylation (to fluoride and dichloroacetic acid [DCAA]). Inorganic fluoride can be toxic, but it remains unknown why other anesthetics, commensurately increasing systemic fluoride concentrations, are not toxic. Fluoride is one of many methoxyflurane metabolites and may itself cause toxicity and/or reflect formation of other toxic metabolite(s). This investigation evaluated the disposition and renal effects of known methoxyflurane metabolites. **METHODS:** Rats were given by intraperitoneal injection the methoxyflurane metabolites MDFA, DCAA, or sodium fluoride (0.22, 0.45, 0.9, or 1.8 mmol/kg followed by 0.11, 0.22, 0.45, or 0.9 mmol/kg on the next 3 days) at doses relevant to metabolite exposure after methoxyflurane anesthesia, or DCAA and fluoride in combination. Renal histology and function (blood urea nitrogen, urine volume, urine osmolality) and metabolite excretion in urine were assessed. **RESULTS:** Methoxyflurane metabolite excretion in urine after injection approximated that after methoxyflurane anesthesia, confirming the appropriateness of metabolite doses. Neither MDFA nor DCAA alone had any effects on renal function parameters or necrosis. Fluoride at low doses (0.22, then 0.11 mmol/kg) decreased osmolality, whereas higher doses (0.45, then 0.22 mmol/kg) also caused diuresis but not significant necrosis. Fluoride and DCAA together caused significantly greater tubular cell necrosis than fluoride alone. **CONCLUSIONS:** Methoxyflurane nephrotoxicity seems to result from O-demethylation, which forms both fluoride and DCAA. Because their co-formation is unique to methoxyflurane compared with other volatile anesthetics and they are more toxic than fluoride alone, this suggests a new hypothesis of methoxyflurane nephrotoxicity. This may explain why increased fluoride formation from methoxyflurane, but not other anesthetics, is associated with toxicity. These results may have implications for the interpretation of clinical anesthetic defluorination, use of volatile anesthetics, and the laboratory methods used to evaluate potential anesthetic toxicity.

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Keywords: Anesthetics; Dechlorination; Defluorination; Dichloroacetic acid; Diuresis; Methoxyflurane metabolism; Nephrotoxicity; O-Demethylation; Osmolality; Rats and methoxyflurane.

Source: Anesthesiology 2006 Oct;105(4):737-45.