Bioavailability of Fluoride in Postmenopausal Women: Comparative Study Between Sodium Fluoride and Disodium Monofluorophosphate-Calcium Carbonate

Frédéric Lioté, Christophe Bardin, Amélie Liou, Agnes Brouard, Jean-Loup Terrier, and Daniel Kuntz
Clinique de Rhumatologie (Centre Viggo Petersen) and Service de Pharmacie, Hôpital Lariboisière, Paris, France

Received December 28, 1990, and in revised form July 19, 1991

Summary. Fluoride (F) increases trabecular bone mass and can be used in the treatment of osteoporosis with crush fractures. As the bioavailability of sodium fluoride (NaF) can be impaired by concomitant absorption of calcium, both drugs have to be ingested separately. However, disodium monofluorophosphate-calcium carbonate (MFP-Ca), another F compound, allows a single administration. In a cross-over randomized study, we compared the bioavailability of both drugs under regular conditions of prescription. Ten postmenopausal women (aged 48–77 years) with glomerular filtration rate (GFR) >70 ml/minute and without bone disease entered the study. Each received 25 mg of NaF [i.e., 11.3 mg F ion (F–)] fasting and 100 mg of Na2FPO3-CaCO3 (i.e., 13.2 mg F–) with breakfast in a single dose separated by an 8-day washout. After dosing, plasma F levels and fractionated and total urinary F collection were determined during a 24-hour period using a specific electrode. Results show a significant shorter lag time absorption (Tmax = 1.4 ± 0.2 hour) and a higher maximal concentration (Cmax = 260 ± 60 ng/ml) for MFP-Ca than for NaF (Tmax = 2.5 ± 0.4 hour; Cmax = 200 ± 85 ng/ml). However, areas under curve (AUC) for MFP-Ca (1711 ± 195 μg/liter/hour) and for NaF (1202 ± 147 μg/liter/hour) were not significantly different. The relative bioavailability of both F compounds related to their fluoride content (i.e., 1.22 for AUC ratio) was equivalent, according to the Westlake method. These data provide the first evidence of comparable bioavailability of two F compounds in a population of postmenopausal women. In addition to the higher Cmax achieved with this compound, it could suggest the use of MFP-Ca as a simple treatment schedule in osteoporosis.

Key words: Fluoride – Bioavailability – Osteoporosis – Menopause.

Chronic fluoride administration increases trabecular bone mass by stimulating bone formation rate [1-3]; therefore, sodium fluoride (NaF) has been reported to be an efficient drug for the treatment of postmenopausal osteoporosis [4]. However, the effect of fluoride on bone strength is a controversial point because the dosage reported in trials ranged from 20 to 200 mg daily [5]. NaF, usually available in plain or enteric-coated tablets, is generally prescribed in association with calcium supplementation [6] to avoid mineralization defect and secondary hyperparathyroidism [7]. As bioavailability of fluor can be impaired by concomitant absorption of Ca, recommendations have been made to ingest both drugs separately [6]; however, compliance to treatment might be reduced because of such a complex treatment schedule. In addition, other causes of impaired bioavailability have been reported, such as food interaction and antiacid administration [8-10]. In order to improve fluor absorption as well as compliance to treatment, another fluoride compound has been designed: disodium monofluorophosphate-calcium carbonate (Na2FPO3-CaCO3, MFP-Ca) which associates both Ca and fluor molecules and allows a single drug administration. In previous comparative studies the bioavailability of MFP-Ca appeared to be better than NaF regarding kinetics and area under curves (AUC). However, these pharmacological studies reported to date have been done in young healthy volunteers, thus leading to possible misinterpretations of results regarding a postmenopausal population in which impaired intestinal absorption cannot be ruled out. Therefore, we have compared the pharmacokinetics and the bioavailability of these two fluoride compounds in postmenopausal women by giving them commercially available compounds according to the conditions of prescription recommended in our country.

Subjects and Methods

Subjects

Ten Caucasian women, aged 48-75 years (mean ± SD, 60.0 ± 6.3) who had reached menopause at least 4 years ago (mean 15.5, range 4–32), entered the study. All gave their consent after information on the aim and design of the study, approved by the Hospital Ethical Committee, had been given. They were admitted to the Department of Rheumatology for osteoarthritis. A complete medical history was obtained from each volunteer and none had clinical evidence of bone disease or endocrinopathy such as thyroid disease, acromegaly, or primary hyperparathyroidism. Individual relevant clinical parameters are presented on Table 1. Renal function was normal in all as defined by a GFR above 70 ml/minute of creatinine (mean GFR = 86.7 ml/minute) (Table 1). Basal serum and urine calcium and phosphate levels were within normal limits. Lateral views of the thoracic and lumbar spine showed no crush fractures. A review of medications was negative for F-containing drugs, F-containing drinking water (Vichy Saint-Yorre), or intake of drugs modifying F absorption (antacids). The subjects were asked not to use F-containing toothpaste 2 days before and during the protocol period.

Drugs

NaF was given in the form of enteric-coated tablets containing 25 mg...
Analytical Methods

Samples were measured according to the analytical technique called “known adding” which is an alternative method useful for measuring concentrations of an ion in the presence of an excess complexing agent. For each sample, three measurements were determined: 100 μl of the sample solution added to either (1) 100 μl of total ionic strength adjustment buffer (TISAB II); or (2) 100 μl of a standard solution containing 200 ng/ml of NaF diluted in TISAB II; or (3) 100 μl of a standard solution containing 300 ng/ml of NaF diluted in TISAB II. The original sample concentration is determined from the change in potential before and after the addition of the standard solution. Standard samples of NaF revealed a linear response from 10⁻⁸ M to 10⁻³ M. The intraassay variation coefficient for fluoride measurement in plasma was 2.3%; the interassay variation coefficients were 4.5 and 4.9% for an aqueous standard solution of 100 ng/ml and 40 ng/ml, respectively.

Pharmacokinetic Analysis

Results are given as mean ± SD. Plasma F concentrations were corrected by subtraction of the baseline values determined at To just before the administration of the drugs. From the individual plasma F concentrations, the following pharmacokinetic parameters were calculated: maximum drug concentration (Cmax), lag time of maximum drug concentration (Tlag), area under the plasma concentration versus time curve from 0 to 24 hours [AUC (0-24)], extrapolated area under the curve [ext AUC (0-∞)]. As fluoride absorption follows first-order kinetics, the AUC (0-24) was calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for declining concentrations. The ext AUC (0-∞) was calculated and added to the AUC (0-24). Ext AUC (0-∞) was obtained with the formula: ext AUC (0-∞) = C/k, in which C is the measured F concentration at the 24th hour and k is the slope obtained from the least-squares linear regression of the terminal points.

The 24-hour urinary excretion of fluoride (Qu) was determined. The recovery of each administered dose was calculated according to the ratio: 24 h urinary excretion/F⁻ intake.

The relative bioavailability between both F compounds was given by the formula:

\[
\frac{AUC (0-∞) MFP-Ca}{D (MFP-Ca)} \times \frac{D (NaF)}{AUC (0-∞)NaF}
\]

where D represents the fluoride element contained in 100 mg of MFP-Ca or 25 mg of NaF (i.e., 13.2 mg F⁻ and 11.3 mg F⁻), respectively. Thus, this method enabled the comparison of the two preparations and their slightly different F-concentrations although an ideal study would have allowed direct comparison in equal dosages.

Statistical Analysis

Statistical analysis was performed using the personal software, BIO-STAT. Pharmacokinetics parameters (Cmax, AUC, Qu) were compared using the analysis of variance (ANOVA) test and the one-tailed paired t test. The Wilcoxon test was used for comparing Tlag. A statistical significance was defined as a P value <0.05. Statistical analysis was improved using the Westlake test offering a 95% confidence interval around the estimated mean of the reference product compared using the analysis of variance (ANOVA) test and the one-asymmetrical interval test. If the latter cannot add a valuable answer to the statistical comparison, the difference in bioavailability of fluoride between the two drugs is only significant when it reaches 25% difference or more. We decided to conclude with the relative bioavailability between the two fluoride salts by accepting a value of 1.25 (25%) [11, 12], as there is no report describing a correlation between an optimal F plasma concentration and an expected optimal pharmacological effect.