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What is This?
Pharmacokinetics of Chronic Fluoride Ingestion in Growing Pigs

A. RICHARDS, J. KRAESTRUP, and F. NIELSEN-KUDSK

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The present study was undertaken to estimate bio-availability and biological half-life of fluoride and accumulation of fluoride in bone in the domestic pig. Eight animals receiving 2 mg F⁻/kg b.w. per day from age 8 to 14 months were compared with eight controls.

Plasma fluoride concentrations just prior to the daily oral dose were measured at regular intervals. After 112 days post-dose, plasma fluoride levels were measured over a 48-hour period following the daily oral dose or a single intravenous dose. Mean bio-availability factor for the oral dose was 0.3 (range 0.2-0.4), and mean biological half-life was 59 days (range 49-72). Bone fluoride content calculated from the pharmacokinetic parameters derived from plasma data was similar to the content of fluoride measured in the bone at slaughter.

The study showed that accumulation of fluoride in bone influences plasma fluoride levels during chronic administration of fluoride to growing pigs. The long biological half-life found showed that it was not possible to achieve steady-state plasma levels within the six-month experimental period used. This means that, for dose-response studies of dental fluorosis in this animal, it is not possible to achieve steady-state plasma concentrations as a basis for correlations to the degrees of pathological change observed in the teeth.


Introduction.

Single-dose studies in man have provided information on bio-availability, absorption, distribution, and renal handling of fluoride. This knowledge has been applied when evaluating acute toxicity of a variety of fluoride preparations used in dentistry (for review, see Ekstrand, 1983). Very little information is available on the pharmacokinetics of chronic fluoride exposure in man or animals.

Compartmental models for describing the pharmacokinetics of chronic fluoride exposure have been proposed on the basis of studies in the rabbit (Hall et al., 1977), rat (Charkes et al., 1979), and man (Ekstrand et al., 1977). These models are based on the concept that fluoride is both taken up by, and released from, the bone pool which, in principle, consists of two compartments: a readily exchangeable one, and one which is very poorly exchangeable in the short term (for review, see Taves and Guy, 1979). In keeping with this concept, experimentally induced increases (PTH) or decreases (calcitonin) in bone resorption have been shown to increase or decrease, respectively, plasma fluoride levels in human subjects (Waterhouse et al., 1980).

During chronic fluoride administration, growth and turnover of bone may therefore be expected to influence plasma fluoride levels. No detailed quantitative investigations of the accumulation of fluoride in bone and its relation to plasma fluoride have hitherto been reported. Studies of this kind involve estimations of the biological half-life, determined from the terminal part of the plasma concentration, versus time curve. This parameter defines the rate of fluoride mobilization from the "deep" bone pool. Estimation of biological half-life is a prerequisite for calculation of the experimental periods necessary to achieve steady-state plasma concentrations.

We are interested in using the pig as an animal model for dose-response studies of dental and osteofluorosis, relating plasma concentrations of fluoride to the severity of the hard tissue lesions.

The purpose of the present experiment was to study the pharmacokinetics of chronic fluoride administration to growing pigs. The first objective was to obtain data on plasma levels in relation to oral dose. Second, the study aimed at estimating bio-availability, biological half-life, and accumulation of the drug.

Materials and methods.

Experimental design. - Sixteen Danish/Danish x Danish/Yorkshire Landrace gilts (four from each of four litters) were studied from age 8 to 14 months. At the beginning of the study period, the pigs were divided according to weight to provide eight experimental and eight control animals. Each group contained two pigs from each litter, and they were all housed in individual sties. Experimental animals were each given 2 mg F⁻/kg b.w. daily as a solution of sodium fluoride together with the morning feed. The dose was adjusted every 14 days according to increases in mean body weight of the pigs given fluoride. In this way, the actual dose of fluoride given throughout the study period to any one animal in the experimental group was kept within the range of 1.9-2.1 mg F⁻/kg b.w. per day. The eight controls received an equivalent quantity of distilled water in a blind design. The study comprised both chronic and single-dose experiments. At intervals during the study period, plasma samples were taken just prior to the daily oral dose for the chronic experiment. Single-dose experiments based on plasma samples taken over a 48-hour period after the daily oral dose, were conducted in the fourth month of the study period.

Diet. - From weaning until slaughter at 14 months, all pigs were fed a specially prepared diet consisting of ground barley (85.4%), soya meal (12%), NaHPO₄ (1.2%), CaCO₃ (0.8%), NaCl (0.4%), and a vitamin supplement (0.2%). The calcium phosphate, calcium carbonate, and sodium chloride were fluoride-free analytical grade chemicals. This reduced the fluoride content of the diet from 25-30 mg F⁻/kg dry feed often occurring in pig feeds (Richards, 1982) to 0.42-0.92 mg F⁻/kg dry feed. From age 8 to 14 months, each animal received 1.25 kg foodstuff together with 3.3 l tap water twice daily. Samples of feed and water were collected every 14 days for analysis of fluoride content. The water contained 0.47-0.56 mg F⁻/l. Fluoride intake from diet (2.5 kg feed + 6.6 l water daily) was therefore less than 0.05 mg F⁻/kg b.w. per day.

Blood samples. - Plasma fluoride concentrations were determined from blood samples (5 ml) drawn from ear veins of both the control and experimental animals just prior to the morning feed. These so-called pre-dose samples

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were taken at intervals throughout the experiment, providing a total of ten samples per animal (cf. Fig. 1). Studies of post-dose plasma fluoride concentrations were carried out in the fourth month of the study when the animals were 12 months old. Six animals from the fluoride group and two from the control group were selected at random for this purpose. At this time, these animals weighed between 150 and 160 kg. An indwelling 30-cm-long polyethylene catheter\(^2\) inserted into an ear vein was used for these plasma samples. Between samplings, the catheter was filled with heparinized, fluoride-free physiological saline. Samples were taken from experimental pigs 0.3, 0.6, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 22, 26, 30, 38, and 48 hours after the oral dose of 2 mg F/kg b.w. (four animals) or after intravenous administration of 0.4 or 0.5 mg F/kg b.w. (two animals), and at three- to four-hour intervals throughout the day from control pigs (two animals).

**Bone samples.**—Fifth lumbar vertebrae and right femurs were obtained at slaughter. Sagittal slices were sawn from the vertebrae and the diaphyses of the femurs and stored at \(-18^\circ\) C. These slices were subsequently used for estimation of fluoride content of cortical (femur) and trabecular (vertebrae) bone.

**Fluoride analyses.**—An ion-specific electrode\(^3\) was used for all fluoride estimations. Plasma was buffered with acetate (Fry and Taves, 1970) and tap water with TISAB.\(^3\) Samples of dry feed (7 g) were weighed and pre-treated with 50 ml of 0.2 M perchloric acid, under constant stirring, for 24 hours. After being centrifuged, 3.0-ml aliquots of the supernatant were added to 0.3 ml of 2 M potassium hydroxide and buffered with TISAB. Bone samples were pulverized and de-fatted in an ether/alcohol mixture for 24 hours and then dried. Weighed portions (10 mg) were dissolved in 1.5 ml of 0.5 M perchloric acid and buffered with 6.0 ml of 0.5 M sodium citrate [modification of method described by McCann (1968)].

**Pharmacokinetics.**—Mean minimum plasma fluoride/time data obtained from the eight experimental pigs during multiple oral ingestions of the daily dose of 2 mg fluoride per kg body weight were corrected by subtraction of the corresponding steady-state data (cf. Fig. 1) obtained from the eight control pigs receiving the low-fluoride diet. The corrected accumulation data were then subjected to iterative non-linear regression analysis using the following model function of accumulation (cf. Gibaldi and Perrier, 1975):

\[
c_{n,\text{min}} = C_{\infty,\text{min}}(1-e^{-k_t n,\text{min}})
\]

where \(c_{n,\text{min}}\) is the pre-dose minimum plasma concentration of fluoride (in mg/l), \(C_{\infty,\text{min}}\) is the steady state concentration corresponding to the above-named daily dose, \(k_t\) is the time in days to the end of dose interval, \(n,\) and \(k_1\) is the apparent terminal elimination constant in days\(^{-1}\).

The apparent volume of distribution was calculated as \(V_{d,\text{area}} = a_0/C_{\infty,\text{min}}\), where \(a_0\) is the minimum accumulated amount of fluoride in the organism at steady state. This in turn is determined as \(a_0 = a_0 e^{-k_t T}(1 - e^{-k_t T})\), where \(a_0\) is the systemic available dose and \(T\) is the dose interval (one day). Plasma clearance was determined as the product of \(V_{d,\text{area}}\) and \(k_1\). The bio-availability factor used (mean, 0.30; SD, 0.09) in the estimation of \(a_0\) was determined as the mean of factors found by non-linear regression analyses of four experimental post-dose data sets (cf. Figs. 3 and 4), the results of which are reported in Table 1. In these experiments, apparent short-term pharmacokinetic parameters of fluoride were determined in the fluoride-exposed pigs after the latest of multiple administrations for 112 days of a single oral dose of 2 mg per kg body weight. Data-sets for non-linear regression analyses were obtained after either intravenous (\(n = 2\)) or oral (\(n = 4\)) single-dose administrations. Corrections of data were performed by subtraction of the steady-state level found in the control pigs. A three-exponential model function could be fitted to both intravenous and oral data, weighted according to the reciprocal of the squares of the experimental values:

\[
c_{n,t} = \sum_{i=1}^{m} A_i e^{-k_i t}
\]

where \(c_{n,t}\) is the plasma fluoride concentration at time, \(t\), during dose interval, \(n\) (cf. Wagner, 1975); \(m = 3\) (number of exponential terms) and the corresponding rate constants of distribution and elimination, \(k_i\), correspond to \(\alpha, \beta,\) and \(\nu\) in the intravenous experiments and \(\alpha, \beta,\) and \(k_3\) in the oral experiments, where \(k_a\) is the absorption rate constant. \(A_i\) are the backward projection concentration constants corresponding to time zero in dose interval \(n\). Single-dose pharmacokinetic parameters were calculated as \(A_i = A_i^{b}(1-e^{-k_i T})/(1-e^{-k_i T})\). \(A_i\)-values were further corrected for intravenous infusion or lag time, followed by determination of AUC, \(V_{d,\text{area}}\), plasma clearance, and systemic availability, according to well-known principles (Wagner, 1975; Nielsen-Kudsk, 1981a&b, 1983a). Non-linear, iterative regression analyses were performed with both NONLIN (Mettler, 1969) and KINON-85, 2 (Nielsen-Kudsk, 1983b).

**Results.**

Mean pre-dose plasma fluoride levels increased from 0.014 mg F\(^{-1}\)l (SD 0.002, \(n = 8\)), prior to the period of fluoride administration, to 0.242 mg F\(^{-1}\)l (SD 0.038, \(n = 8\)) at the end of the experiment. An apparent, mean steady-state plasma fluoride concentration of 0.014 mg/l was ob-

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\(^2\)Bard International, Ltd., Sunderland, England

\(^3\)Orion Res., USA
APPARENT SHORT-TERM FLUORIDE KINETICS AFTER CHRONIC INGESTION OF 2 MG F/KG B.W. DAILY FOR 112 DAYS

<table>
<thead>
<tr>
<th>Pig No.</th>
<th>101</th>
<th>121</th>
<th>156</th>
<th>157</th>
<th>239</th>
<th>94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight in kg</td>
<td>151</td>
<td>160</td>
<td>155</td>
<td>155</td>
<td>150</td>
<td>158</td>
</tr>
<tr>
<td>Dose in mg kg⁻¹</td>
<td>0.50</td>
<td>0.36</td>
<td>1.91</td>
<td>1.91</td>
<td>1.97</td>
<td>1.87</td>
</tr>
<tr>
<td>Mode of administration</td>
<td>i.v.</td>
<td>i.v.</td>
<td>oral</td>
<td>oral</td>
<td>oral</td>
<td>oral</td>
</tr>
<tr>
<td>$\alpha$ hr⁻¹</td>
<td>7.72</td>
<td>7.21</td>
<td>0.32</td>
<td>0.21</td>
<td>0.26</td>
<td>0.29</td>
</tr>
<tr>
<td>$\beta$ hr⁻¹</td>
<td>0.7353</td>
<td>0.7510</td>
<td>0.0061</td>
<td>0.0122</td>
<td>0.0191</td>
<td>0.0162</td>
</tr>
<tr>
<td>$\gamma$ hr⁻¹</td>
<td>3.66</td>
<td>3.97</td>
<td>2.01</td>
<td>2.01</td>
<td>2.01</td>
<td>2.01</td>
</tr>
<tr>
<td>$\nu$ hr⁻¹</td>
<td>0.01557</td>
<td>0.00893</td>
<td>0.113</td>
<td>0.073</td>
<td>0.136</td>
<td>0.43</td>
</tr>
<tr>
<td>t(%) $\beta$ hr</td>
<td>45</td>
<td>78</td>
<td>113</td>
<td>57</td>
<td>36</td>
<td>43</td>
</tr>
<tr>
<td>t(%) $\gamma$ hr</td>
<td>45</td>
<td>78</td>
<td>113</td>
<td>57</td>
<td>36</td>
<td>43</td>
</tr>
<tr>
<td>AUC µg hr⁻¹</td>
<td>6.377</td>
<td>4.444</td>
<td>7.261</td>
<td>7.364</td>
<td>8.494</td>
<td>7.298</td>
</tr>
<tr>
<td>Apparent Vd area lt kg⁻¹</td>
<td>5.036</td>
<td>9.178</td>
<td>9.166</td>
<td>5.037</td>
<td>5.038</td>
<td>5.035</td>
</tr>
<tr>
<td>Apparent Clearance in lt kg⁻¹ hr⁻¹</td>
<td>0.0784</td>
<td>0.0820</td>
<td>0.0562</td>
<td>0.0612</td>
<td>0.0962</td>
<td>0.0816</td>
</tr>
<tr>
<td>Bio-availability, %</td>
<td>100</td>
<td>100</td>
<td>21.4</td>
<td>23.6</td>
<td>41.5</td>
<td>31.8</td>
</tr>
</tbody>
</table>

Corrections were made according to steady-state level in the control pigs and for inter-individual variation in the biological half-lives.

Discussion.

This study has demonstrated a continuous increase in pre-dose plasma fluoride concentrations in growing pigs served for controls (Fig. 1). Body weight of all animals increased continuously throughout the experiment, with no significant differences between mean weight of experimental and control groups (Fig. 2).

Post-dose changes in plasma fluoride concentration after daily single oral doses are illustrated in Fig. 3, together with the within-day measurements for control animals fed the low-fluoride diet.

A computer-generated three-exponential curve of best fit for one (randomly selected) post-dose curve is shown in Fig. 4. Apparent short-term pharmacokinetic parameters calculated from the post-dose studies are shown in Table 1 and parameters for fluoride accumulation in Table 2.

Mean fluoride content of cortical bone from fluoride-treated pigs was 1737 mg/kg (SD 309), as compared with 129 mg/kg (SD 26) in controls, and corresponding values for trabecular bone were 2836 (SD 200) and 181 (SD 16) mg/kg.

**Fig. 2** – Plots of increases in mean body weight of eight growing pigs given 2 mg F/kg b.w. daily (-----) and eight control animals (- - - - -) during the study period from age 8 to 14 months. Vertical bars represent one standard deviation.

**Fig. 3** – Plot of changes in plasma fluoride levels with time, after the daily oral dose of fluoride in four pigs from the experimental group (-----) and after feeding the low-fluoride diet to two control animals (-----).

given 2 mg F⁻/kg. b.w. daily for six months. Peak fluoride concentrations occurred within two hours of administering the daily oral dose, and accumulation of fluoride in bone was shown by the more than 12 times higher fluoride content of bone from experimental animals as compared with controls.

The continuous increase in plasma fluoride with time is consistent with human studies which have reported increasing plasma fluoride levels (Hanhijärvi et al., 1974; Parkins et al., 1974) during long-term fluoride consumption. At the start of the experiment, the mean plasma fluoride concentration for all animals was 0.014 F⁻/ml (0.7 µM/l), and the control animals maintained this level. This is comparable with plasma fluoride levels reported for humans in areas with drinking water containing approximately 0.7 mg F⁻/l (Guy et al., 1976). It is lower than the 0.040 – 0.082 mg/l previously reported for pigs on diets providing 30 mg F⁻/day (Richards et al., 1982) and demonstrates the effectiveness of using the fluoride-free minerals in the specially prepared diet in this study. Plasma concentrations comparable with the 0.242 mg/l (12.7 µM/l) measured at the end of the experiment have been reported for adult humans in an area with 10 mg F/l in the drinking water (Teotia et al., 1976).

The oral dose of 2 mg F⁻/kg b.w. was chosen, since previous studies (Spencer et al., 1971; Richards et al., 1983)
indicated that this dose produces mild degrees of enamel hypomineralization similar to human dental fluorosis. Oral doses of 0.5-0.75 mg/kg b.w. are used in treatment of osteoporosis (Jowsey et al., 1979), and doses of this magnitude may be ingested by people living in areas of endemic fluorosis (Teotia and Teotia, 1973). In man, the bioavailability of these doses can be expected to approach 100% (Ekstrand, 1983).

The bioavailability factor of 0.3 (range 0.2 to 0.4) found for pigs in the present study should be regarded as approximate. These estimates were based only on results from four oral and two intravenous experiments. The data covered the full dose interval (24 hr) and were corrected for inter-individual differences in disposition rate constants, but ideally, the oral and intravenous studies should have been performed on the same animals. In addition, it is possible that the bioavailability may have varied during this chronic experiment. This could possibly be expected as the proportion of fluoride to calcium in the diet increased with time, which, in turn, might have increased bioavailability with time. On the other hand, the concentration gradient for fluoride from stomach to plasma will have decreased with time, which might reduce bioavailability. However, it seems reasonable to assume that the influence of these factors will have been minimal, since similar results (Richards et al., 1982) were obtained when lower doses were given to younger animals on a diet containing an amount of calcium similar to that used in this study.

In the present study, a mean biological half-life for fluoride of 58.5 days (range 49-72 days) was found (Table 2). Half-lives in human plasma have been reported to be in the 3-9-hour range (Ekstrand et al., 1983). From single-dose estimations of this parameter in adult humans, it was shown that the equation proposed by Wagner et al. (1965) could be used to predict experimentally confirmed steady-state plasma levels (Ekstrand et al., 1977). This shorter half-life reported from pharmacokinetic studies in man is still the most significant half-life when considering toxicological aspects of single doses. However, it should be emphasized that the biological half-life for fluoride in man is determined by the elimination rate from the slowest compartment, which belongs to the bone system. The half-life of loss of fluoride from bone to plasma is definitely greater than the 3-9 hours reported by Ekstrand (1983). Longer periods of multiple dosing of the order of months, rather than the six days used by Ekstrand et al. (1977), would probably have demonstrated this. The biological half-life in adult humans could be expected to be of the order of years, in keeping with rates of skeletal turnover (Parfitt, 1983), since fluoride is not likely to be released from deep bone compartments before resorption occurs. This is supported by prolonged increased urinary excretion of fluoride which followed cessation of long periods of fluoride ingestion in man (Largent, 1952). The short fluoride half-lives reported by Ekstrand (1983) must refer to an earlier phase of distribution on the plasma concentration versus time curves. The clearance rates occurring in these phases define the rates at which fluoride enters penultimate compartments, such as urine or readily exchangeable bone, and by definition half-lives from these phases cannot express biological half-life. The same applies to the half-lives of 0.7-1.1 hr previously reported for pigs (Richards et al., 1982).

![Graph](image-url)

Fig. 4 - Computer-generated three-exponential curve of best fit determined by non-linear, iterative regression analysis of post-dose plasma fluoride/time data (after subtraction of pre-dose plasma fluoride concentration) from one of the experimental animals shown in Fig. 3.

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLUORIDE ACCUMULATION PARAMETERS DERIVED BY NON-LINEAR REGRESSION OF MEAN PLASMA FLUORIDE TIME DATA</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Fluoride-exposed Pigs</th>
<th>Control Pigs (calculated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal elimination constant, ( k_1 ) in days(^{-1} )</td>
<td>0.01185 ± 0.00227(^+ )</td>
<td>0.01185 (assumed)</td>
</tr>
<tr>
<td>Biological half-life mean in days</td>
<td>58.49 (49.09 – 72.35)(^++ )</td>
<td>58.49 (assumed)</td>
</tr>
<tr>
<td>Minimum plasma fluoride at steady state, mg 1 lt(^{-1} )</td>
<td>0.237 ± 0.021(^+ )</td>
<td>0.014 ± 0.001(^+ )</td>
</tr>
<tr>
<td>Mean systemic available dose, mg kg(^{-1} )</td>
<td>0.600 (x 1 daily)</td>
<td>0.006 (x 2 daily)</td>
</tr>
<tr>
<td>Plasma fluoride clearance 1 lt kg(^{-1} ) day(^{-1} )</td>
<td>2.52</td>
<td>0.71</td>
</tr>
<tr>
<td>Apparent volume of distribution, ( V_d ) area 1 lt kg(^{-1} )</td>
<td>212.6</td>
<td>60.1</td>
</tr>
<tr>
<td>Minimum cumulated amount of fluoride at steady state, mg kg(^{-1} )</td>
<td>50.38</td>
<td>0.84</td>
</tr>
<tr>
<td>Cumulation index, ( c_{min} ), ( \infty/c_{min} )</td>
<td>84.9</td>
<td>169.3</td>
</tr>
</tbody>
</table>

Data corrected by subtraction of the mean minimum plasma fluoride concentration obtained in control pigs, cf. Fig. 1. The bioavailability factor used (0.30 ± 0.09 SD) was determined as the mean of factors derived from the analyses of four data sets also reported in this paper (cf. Table 1).

\(^+ \) = standard error of mean.

\(^++ \) = range.
For dose-response studies of effects of various levels of plasma fluoride on the mineralizing tissues, it would be ideal if steady-state plasma levels could be achieved. Prediction of conditions necessary to achieve constant plasma levels would require that the relative volume of the bone compartment was constant, which it is not in growing animals. Even if this were the case, the mean half-life of 58 days indicates that steady-state would not be reached in an experimental period of six months.

The increase in pre-dose plasma fluoride concentration with time is due to accumulation of fluoride in the organism, mainly in the deep bone compartment. Another factor which, in theory, may have caused some of this increase in plasma fluoride is a relative decrease in the volume of distribution. Since the dose was constant in terms of mg/kg body weight, the total amount of fluoride given per day increased 50% during the six-month period, in parallel with increasing body weight. This would not have affected plasma concentrations significantly if volume of distribution increased linearly with increase in body weight in these animals. It is not known whether this was the case, since no information is available on the relationship between body weight and volume of distribution in the growing pig, but it seems reasonable to assume that the volume of distribution increased proportional to the increase in body weight. In man, it has been shown that, with the exception of infants, the volume of distribution is closely related to body weight (Gibaldi and Perrier, 1975).

The very large apparent volumes of fluoride distribution (Vd area) found in the chronic cumulation experiments, compared with those determined in the acute post-dose studies, clearly show the necessity of including a fourth exponential term in a model function describing the long-term pharmacokinetics of fluoride in the pig. The lowest composite rate constant (kF) and the corresponding large Vd area are probably related to the bone system (or part of it), which represents a poorly-accessible, deep compartment acting as a main depot for fluoride. The lower Vd area estimated for control pigs, compared with that in fluoride-treated pigs, could possibly reflect a fluoride concentration-related (dose-related) difference in fluoride-binding capacity in growing bone tissue.

Kekki et al. (1982) have postulated, on the basis of graphical analyses of their own experiments in man and results of rabbit studies published by Hall et al. (1977), that fluoride kinetics can be described by a single one-compartment model with non-linear tissue binding, as devised by Wagner (1971). Non-linear parameters, obtained by the graphical methods used, can (if true) be regarded only as preliminary estimates. These methods are very sensitive to errors in the data, and computer-fitting of the data to the model is a prerequisite for obtaining final parameters (cf. Wagner, 1975). The human plasma fluoride/time data depicted by Kekki et al. (1982) in their peroral single-dose fluoride study are not well-defined in the terminal course, and both the absorption and distribution phases are neglected. Interpretation of their findings as evidence for non-linear rather than linear fluoride kinetics thus seems premature and difficult to accept on the basis of the evidence so far reported. Most workers have employed linear pharmacokinetics (Ekstrand et al., 1983), and most recently Fuchs et al. (1984), using linear pharmacokinetics, elegantly demonstrated that dose size is directly related to area under plasma fluoride/time curves in peroral studies in man.

Pharmacokinetic analyses of the plasma data predicted a minimum accumulation of 50 mg F/kg b.w. (cf. Table 2), which would be approximately 8 g per animal (mean weight, 166 kg). Previous studies (Hall et al., 1977) suggest that over 95% of this fluoride will be in bone. Ash weight of bone mineral of the pigs can be estimated on the basis of slaughter analyses (Just Nielsen, 1972), to be in the order of 4 kg. Overall bone F content would accordingly be about 2 g/kg, which is of the same order of magnitude as the directly determined mean fluoride content of 1737 mg/kg in the cortical bone and the 2836 mg/kg in the trabecular bone. Trabecular bone fluoride concentration can be expected to be greater than cortical bone fluoride, since this bone is more accessible for bone plasma exchange than is the cortical bone. The mean fluoride content of the whole skeleton could be expected to be closer to the mean fluoride content of the cortical bone, since the trabecular bone constitutes a smaller fraction of the total bone mass than does the cortical bone. It is not known closely how the chosen sampling sites are representative of total skeletal fluoride. Nonetheless, the similarity of the concentration of bone fluoride calculated from the pharmacokinetic analysis of plasma data and the actual concentrations measured at slaughter suggests that the pharmacokinetic models used are valid.

The total amount of fluoride fed to each experimental pig in the study period was 52.6 g, of which 15.8 g was available for distribution and deposition in the skeleton (bioavailability factor, 0.3). Thus, about 50% (8g) of this fluoride was calculated to be present in the skeleton. Uptake of fluoride to the skeleton has been estimated to be in the order of 50% for adult humans (Hodge et al., 1970) and up to 85% for children (Ekstrand et al., 1981). It seems likely that the net uptake, as a proportion of the available dose, will have been greater at the beginning of this study, since the bone will be less fluoride-saturated with respect to plasma fluoride at this stage. As time progressed, net uptake would be less because the concentration gradient from plasma to bone would be reduced, and loss of fluoride from the deep compartment of bone to plasma, at resorption sites, would play an increasing role with increasing bone mass.

This experiment has provided estimates of pharmacokinetic parameters applicable when using the pig for studies of skeletal and dental fluorosis. The long biological half-life recorded indicates that it would not be possible to achieve steady-state plasma fluoride levels for plasma concentration-response studies within a six-month period, which is when the teeth are developing (Richards, 1982). A more fruitful approach would presumably be to relate fluorotic changes to areas under plasma fluoride concentration/time curves related to various constant doses and dose-time intervals. This would also be more relevant to changes in the pattern of plasma fluoride likely to occur in children or young animals exposed to various concentrations of fluoride in drinking water.

Acknowledgments.

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